FORM PTO-1390 (REV 10-95) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER: IVD 924

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

U. S. APPLICATION NO. (If known, see 37 CFR 1.5): 09/077817

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/FR96/01756	November 7, 1996	December 6, 1995

TITLE OF INVENTION

IL-13 RECEPTOR

APPLICANT(S) FOR DO/EO/US

Daniel Caput, Pascual Ferrara, Patrick Laurent and Natalio Vita

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND or SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1)).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371 (c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☒ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☒ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☒ An unsigned oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. ☒ A FIRST preliminary amendment.

    ☐ A SECOND or SUBSEQUENT preliminary amendment.

14. ☐ A substitute specification.

15. ☐ A change of power of attorney and/or address letter.

16. ☐ Other items or information:

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO **PCT/FR96/01756**	ATTORNEY'S DOCKET NUMBER **IVD 924**

17. ☒ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1. 492 (a)(1)-(5)):

Search Report has been prepared by the EPO or JPO. $930.00
International preliminary examination fee paid to USPTO (37CFR 1.482) $720.00
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) $790.00
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO $1,070.00
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4). $98.00

CALCULATIONS PTO USE ONLY

ENTER APPROPRIATE BASIC FEE AMOUNT =				**$ 930.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ]20 [ ]30 months from the earliest claimed priority date (37 CFR 1.492(e)).				$	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	67-20 =	47	x $22.00	**$1034.00**	
Independent claims	3- 3 =	0	x $82.00	$ -	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $270.00	**$ 270.00**	
TOTAL OF ABOVE CALCULATIONS =				**$2234.00**	
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).				$	
SUBTOTAL =				**$2234.00**	
Processing fee of **$130.00** for furnishing the English translation later than [ ]20 [ ]30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +				$	
TOTAL NATIONAL FEE =				**$2234.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
TOTAL FEES ENCLOSED =				**$2234.00**	
				Amount to be refunded:	$
				Charged	**$2234.00**

a. ☐ A check in the amount of $_____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. **19-0091** in the amount of **$2234.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **19-0091**. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Filing under 35 U.S.C. § 371
Corresponding to International Application Serial No.:
PCT/FR96/01756

Applicant: Daniel Caput, Pascual Ferrara, Patrick Laurent and Natalio Vita

International Filing Date: November 7, 1996

For: IL-13 RECEPTOR

CERTIFICATE UNDER 37 C.F.R. 1.10

Express Mail Label Number: EM317281127US

Date of Deposit: 03 June 1998

I hereby certify that this paper is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" Service on the date indicated above and is addressed to: Asst. Commissioner for Patents, Box PCT, Attn: EO/US, Washington, DC 20231.

Joan M. Hylander

Signature

Assistant Commissioner for Patents
Box PCT
Attn: EO/US
Washington, D.C. 20231

Dear Sir:

PRELIMINARY AMENDMENT

Please amend the above-identified application as follows:

In the Claims

Please amend the claims as follows before calculating the filing fee for the above-identified application:

In claim 5, line 2, rewrite "any one of claims 1 to 4" as -- claim 1 --.

In claim 11, line 2, rewrite "any one of claims 8 to 10" as -- claim 8 --.

In claim 14, lines 2-3, rewrite "any one of claims 5 to 7 and 11 to 13" as -- any one of claims 5 or 11 --.

In claim 16, line 2, rewrite "claims 14 or 15" as -- claim 14 --.

In claim 18, line 3, rewrite "claims 5 to 7" as -- claim 5 --.

In claim 21, line 3, rewrite "claims 11 to 13" as -- claim 11 --.

In claim 24, lines 3 and 6, rewrite " claims 1 to 4 and 8 to 10" as -- claims 1 or 8 --.

In claim 25, line 2, rewrite "5 to 7 and 11 to 13" as -- 5 or 11 --.

In claim 26, lines 1-2, rewrite "claims 18 to 23" as -- claims 18, 21 or 23 --.

In claim 26, lines 4-5, rewrite "claims 1 to 4 or 8 to 10" as -- claims 1 or 8 --.

In claim 27 lines 1-2, rewrite "claims 18 to 23" as -- claims 18, 21 or 23 --.

In claim 28, lines 4-5, rewrite "claims 1 to 4 or 8 to 10" as -- claims 1 or 8 --.

In claim 28, line 7, rewrite "claims 18 to 23" as -- claims 18, 21 or 23 --.

In claim 29, line 2, rewrite "claims 5 to 7 and 11 to 13" as -- claims 5 or 11 --.

In claim 29, line 4, rewrite "1 to 4 and 8 to 10" as -- 1 or 8 --.

In claim 31, line 4-5, rewrite "claims 1 to 4 and 8 to 10" as -- claims 1 or 8 --.

In claim 32, line 3, rewrite "claims 1 to 4 and 8 to 10" as -- claims 1 or 8 --.

In claim 36, line 2, rewrite "claims 1 to 4 or 8 to 10" as -- claims 1 or 8 --.

In claim 37, line 3, rewrite "1 to 4 or 8 to 10" as -- 1, 4, 8 or 10 --.

In claim 39, lines 1-2, rewrite "any one of claims 1 to 4" as -- claim 1 --.

In claim 40, lines 1-2, rewrite "any one of claims 8 to 10" as -- claim 8 --.

In claim 41, lines 1-2, rewrite "any one of claims 1 to 4" as -- claim 1 --.

In claim 42, lines 1-2, rewrite "any one of claims 8 to 10" as -- claim 8 --.

REMARKS

The claims have been amended in order to limit the multiple dependencies of the claims.

Date: June 3, 1998

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ENGLISH TRANSLATION OF INTERNATIONAL PATENT

APPLICATION PCT/FR96/01756

filed on November 7, 1996

in the name of SANOFI

The present invention relates to purified polypeptides having a receptor activity specific for interleukin-13 (IL-13), to their biologically active fragments and to the corresponding nucleic acid sequences and to their applications.

IL-13 is a recently identified (1,2) cytokine of 112 amino acids secreted by the activated T lymphocytes, the B lymphocytes and the mastocytes after activation.

By virtue of its numerous biological properties shared with IL-4, IL-13 has been described as an IL-4-like cytokine. Its activities are indeed similar to those of IL-4 on the B cells (3-5), the monocytes (6-10) and other non-haematopoietic cells (11-12). On the other hand, contrary to IL-4, it would not exert a specific effect on resting or activated T cells (13).

Various biological activities of IL-13 on the monocytes/macrophages, the B lymphocytes and certain haematopoietic precursors have been described in detail by A.J.Minty, as well as in review articles on IL-13 (see for example 14). Several data indicate, in addition, that this cytokine has a pleiotropic effect on other cell types. These non-haematopoietic cells which are directly affected by IL-13 are endothelial and microglial cells, keratinocytes and kidney and colon carcinomas.

The anti-inflammatory and immunoregulatory activities of IL-13 may be useful, for example, in the treatment of autoimmune, tumour and viral pathologies.

An exploitation of these biological properties at the clinical level requires, however, a perfect knowledge of the signals and mechanisms via which these effects are exerted, so as to be able to control and modulate them in the relevant pathologies.

One of the stages in the analysis of the signal transmitted by a biological molecule within a cell consists in identifying its membrane receptor. The research studies carried out to this end on the IL-13 receptor have shown that IL-13 and IL-4 had a common receptor, or at the very least some of the components of a common receptor complex, as well as common signal

transduction elements (15-18). This receptor is present at the surface of various cell types, in a variable number according to the cell type considered. The comparative distribution of the IL-13 and IL-4 receptors has been indicated by A.J.Minty (14).

Kondo et al. (19) have described the structure of a receptor having a high affinity for IL-4. This receptor is a dimer, formed by the association of a glycoprotein of 140 kDa (IL-4R) and of the γ chain of the IL-2 receptor (γc). IL-4 can bind to the glycoprotein subunit of 140 kDa (IL-4R or gp 140) with a high affinity (Kd between 50 and 100 pM) (15). However, this affinity is increased by a factor of 2 to 3 when the γc chain is associated with gp 140. This association is, in addition, necessary for the transmission of certain signals mediated by IL-4 (19,20).

Cross-competition experiments for binding either of IL-13 or of IL-4 have demonstrated that IL-4 can normally prevent the binding of IL-13, whereas IL-13 can generally only partially prevent the binding of IL4 to its receptor (17,21) and does not attach to any of the two subunits of the IL-4 receptor or to the complex formed by their association. On the basis of these observations, the authors of the present invention have assumed that the receptor specific for IL-13 consisted of the receptor complex IL-4 associated with another IL-13 binding component (IL-13Rβ).

Research studies carried out on an erythroleukemic cell line capable of proliferating in response to IL-13 and IL-4 (TF-1 line) allowed them to show that these two cytokines produced similar intracellular events after attachment to their receptor (18). In parallel, cross-linking experiments allowed them to show that gp 140 could form heterodimers either with the γ chain, or with a new subunit, of a molecular weight of 55 to 70 kDa (17,21).

Moreover, research studies recently carried out on a mouse embryonic stem cell line have made it possible to isolate the genomic DNA and the cDNA encoding a

polypeptide of 424 amino acid residues (IL-13Rα), suggesting that the IL-13 receptor shared with the IL-4 receptor a common chain so as to constitute a high-affinity receptor (22, 23), that is to say has an affinity whose constant Kd is situated between values of between about 10 pM and 100 pM (a low-affinity receptor having a constant Kd situated between the values of between 2 nM and 10 nM).

Given the importance, at the medical level, of the fine understanding of the phenomena of regulation of IL-4 and of IL-13, and in particular of the possibility of being able to separate and control separately the effects produced by either of these two cytokines, the authors of the present invention were interested on the one hand, in the characterization of a polypeptide specifically binding IL-13 with a high affinity and, on the other hand, in the characterization of another polypeptide which, alone, specifically binds IL-13 with a low affinity and which, if it is associated with the IL-4 receptor, constitutes a high-affinity receptor for IL-13.

These authors have now identified a human carcinoma cell line expressing the IL-13 specific receptor in a quantity greater than other known human renal carcinoma lines (21), and have now carried out the cloning of the primary subunit responsible for the attachment of IL-13 to the IL-4/IL-13 receptor, called IL-13Rβ, as well as the cloning of the common chain shared by the IL-13 receptor and the IL-4 receptor in order to constitute a high-affinity receptor which allows cross-competition between the 2 cytokines, called IL-13Rα. The present invention therefore relates to purified polypeptides specifically linking IL-13.

More particularly, the subject of the invention is purified polypeptides whose amino acid sequences correspond to that of a receptor specific for IL-13 (IL-13Rβ and IL-13Rα), or biologically active fragments thereof.

The subject of the invention is also isolated DNA

sequences encoding the said polypeptides or their biologically active fragments.

It relates, in addition, to the expression vectors containing at least one of the nucleotide sequences defined above, and the host cells transfected with these expression vectors under conditions allowing the replication and/or expression of one of the said nucleotide sequences.

The methods for producing recombinant IL-13Rβ and IL-13Rα or their biological active fragments by the transfected host cells are also part of the invention.

The invention also comprises pharmaceutical compositions comprising IL-13Rβ and/or IL-13Rα or biologically active fragments thereof for the regulation of the immunological and inflammatory mechanisms produced by IL-13. It relates, in addition, to a method for the identification of agents capable of modulating the activity of IL-13Rβ and/or IL-13Rα, and the use of IL-R13β and/or IL-13Rα or of fragments thereof for screening these agents as well as for the manufacture of new products capable of modulating the activity of the IL-13 receptor.

The invention also comprises antibodies or derivatives of antibodies specific for IL-13Rβ and/or IL-13Rα.

Finally, it relates to a method of therapeutic treatment for modulating the immunological reactions mediated by IL-13, comprising the administration, to a patient, of IL-13Rβ and/or IL-13Rα or of one of their biologically active fragments or of a compound capable of specifically modulating the activity of this receptor, in combination with a pharmaceutically acceptable vehicle.

In the description of the invention below, the following definitions are used:

- polypeptide specifically binding IL-13 with a high affinity (IL-13Rß): a polypeptide comprising the amino acid sequence SEQ ID No. 2 or any biologically active fragment or derivative thereof;
- polypeptide which, alone, specifically binds IL-13 with

a low affinity and which, if it is associated with the IL-4 receptor, constitutes a high-affinity receptor (IL-13Rα) : a polypeptide comprising the amino acid sequence SEQ ID NO 4 or any biologically active fragment or derivative thereof ;

- biologically active: capable of binding specifically to IL-13 and/or of participating in the transduction of the signal specifically produced by IL-13 at the level of the cell membrane, and/or capable of interacting with the receptor specific for IL-4 (IL-4R/gp 140) so as to form a complex capable of binding IL-4 and IL-13, and/or which is recognized by antibodies specific to the polypeptide of sequence SEQ ID No. 2 and/or of sequence SEQ ID No. 4, and/or capable of inducing antibodies which recognize the polypeptide of sequence SEQ ID No. 2 and/or of sequence SEQ ID No. 4;

- derivative: any polypeptide which is a variant of the polypeptide of sequence SEQ ID No. 2 and/or of sequence SEQ ID No. 4, or any molecule resulting from a modification of a genetic and/or chemical nature of the sequence SEQ ID No. 2 or of sequence SEQ ID No. 4, that is to say which is obtained by mutation, deletion, addition, substitution and/or chemical modification of one or of a limited number of amino acids, as well as any isoform sequence, that is to say a sequence which is identical to the sequence SEQ ID No. 2 or to the sequence SEQ ID No. 4, to one of their fragments or to one of their modified sequences, containing one or more amino acids in the D enantiomer form, the said variant, modified or isoform sequences having conserved at least one of the properties which make them biologically active.

The subject of the present invention is a purified polypeptide comprising an amino acid sequence chosen from:

a) the sequence SEQ ID No. 2 or the sequence SEQ ID No. 4,

b) any biologically active sequence derived from SEQ ID No. 2 or SEQ ID No. 4, according to the definition given above.

The manufacture of derivatives may have various objectives, including in particular that of increasing the affinity of the receptor for IL-13, that of modulating the cross-competition between IL-13 and IL-4, that of enhancing their levels of production, of increasing their resistance to proteases, of modifying their biological activity or of conferring new pharmaceutical and/or biological properties on them.

Among biologically active variants of the polypeptides as defined above, the fragments produced by alternate splicing of the transcripts (messenger RNAs) of the gene encoding one of the amino acid sequences described above are preferred.

In an advantageous variant, the 8 C-terminal amino acids of the polypeptide of sequence SEQ ID No. 2 are substituted by the following 6 amino acids: VRCVTL.

According to another advantageous aspect, the invention relates to a soluble form of IL-13Rβ, called IL-13Rβs, comprising especially the extracelluar domain of the polypeptide of sequence SEQ ID No. 2 stretching up to residue 343 and preferably up to residue 337 as well as a soluble form of IL-13Rα, called IL-13Rαs, comprising especially the extracelluar domain of the polypeptide of sequence SEQ ID No. 4 stretching up to residue 343 and preferably up to the residues between 336 and 342.

The polypeptide which comprises the sequence SEQ ID No. 2 or the sequence SEQ ID No. 4 represents a specific embodiment of the invention. As will emerge in the examples, this polypeptide may be expressed at the surface of human cells so as to form a functional IL-13 receptor and/or combine with the IL-4 receptor so as to form, with the γ chain of the IL-2 receptor, the receptor complex common to IL-4 and IL-13.

The subject of the present invention is also an isolated nucleic acid sequence, chosen from:

a) the sequence SEQ ID No. 1,
b) the sequence SEQ ID No. 3,
c) the nucleic acid sequences capable of hybridizing to the sequence SEQ ID No. 1 or to the sequence SEQ ID

No. 3, or to their complementary sequences and encoding polypeptides having an IL-13 receptor activity, or allowing the reconstitution of a receptor having a high affinity for IL-13 and IL-4,

d) the nucleic acid sequences derived from the sequences a) and b) and c) because of the degeneracy of the genetic code.

More particularly, the subject of the invention is a sequence encoding the soluble part of IL-13Rβ or of IL-13Rα and any variant produced by alternate splicing of the transcripts of IL-13Rβ or of IL-13Rα, conserving at least one of the biological properties described.

A preferred embodiment is represented by a nucleic acid sequence comprising or consisting of the stretch of nucleotides stretching from nucleotide No. 1 up to nucleotide 1081, and preferably up to nucleotide 1063 on the sequence SEQ ID No. 1.

Another preferred embodiment is represented by a nucleic acid sequence comprising or consisting of the stretch of nucleotides stretching from nucleotide No. 1 up to nucleotide No. 1059, and preferably up to the nucleotides between numbers 1041 and 1056 on the sequence SEQ ID No. 3.

Advantageously, the nucleic acid sequence according to the invention is a sequence encoding a protein corresponding to the mature form of IL-13Rβ or of IL-13Rα, this mature protein being the result of the release of the signal peptide.

The various nucleotide sequences of the invention may be of artificial origin or otherwise. They may be DNA or RNA sequences obtained by screening sequence libraries by means of probes produced on the basis of the sequence SEQ ID No. 1 or of the sequence SEQ ID No. 3. Such libraries may be prepared by conventional molecular biology techniques known to persons skilled in the art.

The nucleotide sequences according to the invention may also be prepared by chemical synthesis or alternatively by a combination of methods including chemical or enzymatic modification of sequences obtained

by screening of the libraries.

These nucleotide sequences allow the preparation of nucleotide probes encoding a polypeptide according to the invention or a biologically active fragment thereof. The appropriate hybridization conditions correspond to the temperature and ionic strength conditions customarily used by persons skilled in the art, preferably to temperature conditions of between T_m - 5°C and T_m - 30°C and still more preferably, to temperature conditions between T_m - 5°C and T_m - 10°C (high stringency), T_m being the melting temperature, defined as the temperature at which 50 % of the base-paired strands separate. Such probes are also part of the invention. They may be used as a *IN VITRO* diagnostic tool for the detection, by hybridization experiments, of transcripts specific for the polypeptides of the invention in biological samples or for the detection of aberrant syntheses or of genetic abnormalities resulting from a polymorphism, from mutations or from a poor splicing.

The probes of the invention comprise at least 10 nucleotides, and comprise at most the entire nucleotide sequence SEQ ID No. 1 or the entire nucleotide sequence SEQ ID No. 3 or their complementary strand.

Among the shortest probes, that is to say of about 10 to 15 nucleotides, the appropriate hybridization conditions correspond to the temperature and ionic strength conditions customarily used by persons skilled in the art.

Preferably, the probes of the invention are labelled prior to their use. For that, several techniques are within the capability of persons skilled in the art, such as for example fluorescent, radioactive, chemiluminescent or enzymatic labelling.

The *IN VITRO* diagnostic methods in which these nucleotide probes are used for the detection of aberrant syntheses or of genetic abnormalities, such as the loss of heterozygosity and genetic rearrangement, at the level of the nucleic sequences encoding an IL-13 receptor polypeptide or a biologically active fragment, are

included in the present invention. Such a type of method comprises:

- bringing a nucleotide probe of the invention into contact with a biological sample under conditions allowing the formation of a hybridization complex between the said probe and the above-mentioned nucleotide sequence, optionally after a preliminary step of amplification of the abovementioned nucleotide sequence;
- detection of the hybridization complex which may be formed;
- optionally, sequencing the nucleotide sequence forming the hybridization complex with the probe of the invention.

The cDNA probes of the invention may, in addition, be advantageously used for the detection of chromosomal abnormalities.

The nucleotide sequences of the invention are also useful for the manufacture and the use of sense and/or antisense oligonucleotide primers for sequencing reactions or for specific amplification reactions according to the so-called PCR (polymerase chain reaction) technique or any other variant thereof.

The nucleotide sequences according to the invention have, moreover, uses in the therapeutic field for the preparation of antisense sequences which are capable of hybridizing specifically with a nucleic acid sequence, including a messenger RNA, and may be used in gene therapy. The subject of the invention is thus antisense sequences capable of inhibiting, at least partially, the production of IL-13 receptor polypeptides as defined above. Such sequences advantageously consist of those which constitute the reading frame encoding IL-13Rβ or IL-13Rα at the level of the transcript.

They may be more particularly used in the treatment of allergies and of inflammation.

The nucleotide sequences according to the invention may, moreover, be used for the production of recombinant polypeptides, as defined above, having an IL-13 receptor activity.

These polypeptides may be produced from the nucleotide sequences defined above, according to techniques for the production of recombinant products known to persons skilled in the art. In this case, the nucleotide sequence used is placed under the control of signals allowing its expression in a cellular host. The cellular host used may be chosen from prokaryotic systems, such as bacteria, or from eukaryotic systems, such as yeasts, insect cells, CHO cells (chinese hamster ovary cells) or any other system which is advantageously available commercially. A cellular host preferred for the expression of the polypeptides of the invention consists of the fibroblast line COS-7 or COS-3.

The signals controlling the expression of the polypeptides, such as the promoters, the activators or the terminal sequences, are chosen according to the cellular host used. To this end, the nucleotide sequences according to the invention may be inserted into autonomously replicating vectors within the chosen host, or integrative vectors of the chosen host. Such vectors will be prepared according to the methods commonly used by persons skilled in the art, and the resulting clones may be introduced into an appropriate host by standard methods, such as for example electroporation.

The expression vectors containing at least one of the nucleotide sequences defined above are also part of the present invention.

In the case of the COS-7 or COS-3 cells, the transfection may be carried out using the vector pSE-1, as described in (17).

The invention relates, in addition, to the host cells transfected by these expression vectors. These cells may be obtained by the introduction, into host cells, of a nucleotide sequence inserted into a vector as defined above, followed by the culture of the said cells under conditions allowing the replication and/or expression of the transfected nucleotide sequence.

These cells may be used in a method for the production of a recombinant polypeptide of sequence SEQ

ID No. 2 or SEQ ID No. 4 or a derivative, which method is itself included in the present invention and is characterized in that the transfected cells are cultured under conditions allowing the expression of a recombinant polypeptide of sequence SEQ ID No. 2 or SEQ ID No. 4, or a derivative, and in that the said recombinant polypeptide is recovered.

The purification processes used are known to persons skilled in the art. The recombinant polypeptide may be purified from cell lysates and extracts, from the culture supernatant, by methods used individually or in combination, such as fractionation, chromatographic methods, immunoaffinity techniques using specific mono- or polyclonal antibodies.

The mono- or polyclonal antibodies capable of specifically recognizing IL-13Rβ and/or IL-13Rα according to the definition given above are also part of the invention. Polyclonal antibodies may be obtained from the serum of an animal immunized against IL-13Rβ and/or IL-13Rα according to the usual procedures.

The monoclonal antibodies may be obtained according to the conventional hybridoma culture method described by Köhler and Milstein (Nature, 1975, *256*, 495-497).

Advantageous antibodies are antibodies directed against the extracelluar domain of IL-13Rβ and/or IL-13Rα.

The antibodies according to the invention are, for example, chimeric antibodies, humanized antibodies, Fab and F(ab')2 fragments. They may also exist in the form of labelled antibodies or immunoconjugates. For example, they may be associated with a toxin, such as the diphtheria toxin or with a radioactive product. These immunotoxins may in this case constitute therapeutic agents which may be used for the treatment of certain pathologies involving an overexpression of IL-13Rβ and/or IL-13Rα.

The antibodies of the invention, in particular the monoclonal antibodies, may also be used for the

immunocytochemical analyses of the IL-13 receptors on specific tissue sections, for example by immunofluorescence or by gold or peroxidase labelling.

They may be advantageously used in any situation where the expression of IL-13Rβ and/or IL-13Rα needs to be observed, such as for example an abnormal overexpression or the monitoring of the regulation of membrane expression.

The invention therefore also relates to a process for the *IN VITRO* diagnosis of pathologies correlated with an abnormal expression of IL-13Rβ and/or of IL-13Rα, in biological samples capable of containing IL-13Rβ and/or IL-13Rα expressed at an abnormal level, characterized in that at least one antibody of the invention is brought into contact with the said biological sample, under conditions allowing the possible formation of specific immunological complexes between IL-13Rβ and/or of IL-13Rα and the said antibody(ies) and in that the specific immunological complexes which may be formed are detected.

The invention also relates to a kit for the *IN VITRO* diagnosis of an abnormal expression of IL-13Rβ and/or of IL-13Rα in a biological sample and/or for measuring the level of expression of the IL-13 receptor in the said sample comprising:

- at least one antibody specific for IL-13Rβ and/or IL-13Rα, optionally attached onto a support,
- means for revealing the formation of specific antigen/antibody complexes between IL-13Rβ and/or IL-13Rα and the said antibody(ies) and/or means for quantifying these complexes.

Another subject of the invention relates to a method for the identification and/or isolation of ligands specific for IL-13Rβ and/or IL-13Rα or agents capable of modulating its activity, characterized in that a compound or a mixture containing various compounds, optionally nonidentified, is brought into contact with cells expressing at their surface IL-13Rβ and/or IL-13Rα, under conditions allowing interaction between the IL-13 receptor and the said compound, in the case where the

latter would have an affinity for the receptor, and in that the compounds bound to IL-13Rβ and/or IL-13Rα, or those capable of modulating the biological activity thereof, are detected and/or isolated.

In a specific embodiment, this method of the invention is adapted to the identification and/or isolation of agonists and of antagonists of IL-13 for its IL-13Rß and/or IL-13Rα receptor.

The invention also comprises pharmaceutical compositions comprising, as active ingredient, a polypeptide corresponding to the preceding definitions, preferably in a soluble form, combined with a pharmaceutically acceptable vehicle.

Such a polypeptide may indeed act in competition with IL-13Rβ and/or IL-13Rα expressed at the cell surface, and thereby constitute an antagonist specific for the binding of IL-13 to its receptor, which may be advantageously used for the synthesis of a medicinal product intended for modulating the reactions mediated by IL-13 in pathological situations.

Finally, the invention comprises a method for the therapeutic treatment of conditions linked to immunological reactions mediated by IL-13, comprising the administration to a patient of IL-13Rβ and/or IL-13Rα (or of one of their biologically active fragments), or of a compound capable of specifically modulating the biological activity thereof, in combination with a pharmaceutically acceptable vehicle.

Other characteristics and advantages of the invention will emerge in the rest of the description with the examples and the figures, of which the legends are represented below.

LEGEND TO THE FIGURES

- Figure 1: characterization of the human IL-13Rβ receptor present in Caki-1 cells.

a) Scatchard analysis (inset) of the saturation curve of IL-13 labelled with [^{125}I];

b) binding of [^{125}I][Phe43]-IL-13-GlyTyrGlyTyr in the

presence of increasing concentrations of unlabelled IL-13 (·) and of IL-4 (o);

c) cross-linking experiments using radioactive IL-13 in the absence (lane a) and in the presence of a one hundred times excess of unlabelled IL-13 (lane b) or of IL-4 (lane c);

d) inhibition of the secretion of IL-6 induced by IL-13 and IL-4 in the presence of a monoclonal antibody specific for the IL-4R chain and the IL-4 antagonist Y124DIL-4.

- Figure 2: Nucleotide sequence of the cDNA of IL-13Rβ, and comparison of the protein sequences of IL-5R and IL-13Rβ.

a) nucleotide sequence of the cDNA of IL-13Rβ. The amino acids corresponding to the deduced signal peptide of the nucleic sequence are indicated in italics and those corresponding to the transmembrane domain are indicated in bold characters. The potential N-glycosylation sites (Asn-X-Ser/Thr) are underlined;

b) alignment of the amino acids of the IL-13Rβ and IL-5R sequences. The protein sequences of IL-13R and IL-5R are aligned as described above (24). The cysteine residues and the WSXWS motif which are characteristic of this family of receptors are boxed.

- Figure 3: patterns of expression of the IL-13Rβ mRNA.

The RNA was prepared from the following cells: Caki-1 (lane a), A431 (lane b), TF-1 (lane c), U937 (lane d), Jurkat (line e) and IM9 (lane f).

- Figure 4: characterization of the recombinant IL-13Rβ receptor for IL-13. The COS-7 cells are transfected with IL-13Rβ cDNA and used for:

a) studies for the binding of radiolabelled IL-13 (inset) by Scatchard analysis of the saturation curve;

b) cross-linking experiments using radiolabelled IL-13 in the absence (lane a) and in the presence of a one hundred times excess of unlabelled IL-13 (lane b);

c-d) cotransfection experiments using cloned IL-13Rβ, IL-4R (gp140) and the γc chain followed by the binding of

radiolabelled IL-13 (c) or of IL-4 (d). The black and white columns represent the specific binding of IL-13 and of IL-4 respectively.

- Figure 5: inhibition of the binding of IL-13 to IL-13Rβ by the soluble form of the receptor (IL-13Rβs) in transient expression.

The expression of IL-13Rβs in the supernatant of the cells transfected with 2034 is tested by inhibition of the binding of IL-13 on cells transfected with IL-13Rβ (2036). The supernatants are tested in the crude state by diluting them one half in the iodinated ligand.

2036 NSB: nonspecific binding in the presence of an excess of unlabelled IL-13.

2036 BT: total binding on cells transfected with 2036

2036 + sgt 2034: binding to cells transfected with 2036 in the presence of supernatant of cells transfected with 2034.

2036 + sgt pSE1 : control

- Figure 6: inhibition of the binding of IL-13 to IL-13Rβ by the soluble form of the receptor (IL-13Rβs) on stable lines.

T2036-22: total binding on the clone IL-13Rβ (2036-22) in the absence of supernatant of clone secreting IL-13Rßs (reference 100%)

2034-4

2034-6

2034-19 4 clones IL-13Rβs

2034-21

1274-20: in the presence of supernatant of CHO cells not expressing IL-13Rβs (control).

- Figure 7: nucleotide sequence of the IL-13Rα cDNA and comparison of the protein sequences of human IL-13Rα and of murine IL-13Rα.

a) Nucleotide sequence of the IL-13Rα cDNA. The amino acids corresponding to the signal peptide deduced from the nucleic sequence are underlined with a dotted line and those corresponding to the transmembrane domain are underlined with a double line. The potential N-glycosylation sites (Asn-X-Ser/Thr) are boxed.

b) Alignment of the amino acids of human IL-13Rα and of murine IL-13Rα. The protein sequences of human IL-13Rα and of murine IL-13Rα are aligned as described above (24). The cysteine residues and the motif WSXWS which are characteristic of this family of receptors are boxed.

- Figure 8: characterization of the recombinant IL-13Rα receptor for IL-13.

The CHO or COS-3 cells transfected with the IL-13Rα and/or IL-4R cDNA and used for:

a) studies of the binding of iodine-125 labelled IL-13 by Scatchard analysis of the saturation curve with CHO cells transfected with IL-13Rβ cDNA (Figure A), transfected with IL-13Rß cDNA and IL-4R cDNA (Figure B), transfected with IL-13Rα cDNA (Figure C) and transfected with IL-13Rα cDNA and IL-4R cDNA (Figure D),

b) competition experiments of binding of [^{125}I]-IL-13 on CHO cells transfected with IL-13Rß cDNA (Figure E), transfected with IL-13Rß cDNA and IL-4R cDNA (Figure F), transfected with IL-13Rα cDNA (Figure G) and transfected with IL-13Rα cDNA and IL-4R cDNA (Figure H). The white and shaded columns represent respectively the specific binding of radiolabelled IL-13 in the presence of an excess (1,000 times more) of IL-13 or IL-4, the black columns represent total binding.

- Figure 9: comparison of the electrophoretic mobility in EMSA of cellular extracts expressing the receptor for IL-4 alone (CHO-4), the receptor for IL-13Rα alone (CHO-13) or the combined receptors IL-13Rα and IL-4R (CHO-4-13) after activation of the CHO cells in the presence of IL-4 or IL-13 (4 or 13), c representing the nonactivated control.

MATERIALS AND METHODS

Binding and cross-linking experiments:

The binding and cross-linking experiments are carried out as described for [^{125}I][Phe43]-IL-13-GlyTyrGlyTyr (17).

Induction of the secretion of IL-6:

The Caki-1 cells (ATCC HTB46) are placed in 24-well plates at a density of 5×10^4 cells/well and after 3 days of culture, confluent monolayers are washed three times with DMEM medium without foetal calf serum. The stimulation of the Caki-1 cells is carried out with 30 ng/ml of IL-4 or of IL-13 in the absence or in the presence of Y124DIL-4 or of an anti-gp140 monoclonal antibody. The quantity of IL-6 released into the culture medium after incubating for 24 hours is measured by an ELISA technique (Innotest, France).

Isolation and analysis of the human IL-13Rβ cDNA:

Total RNA was extracted from the Caki-1 cells as described above (25). The poly(A) RNA is isolated from the total RNAs with magnetic beads coated with oligo$(dT)_{25}$ (Dynal). A cDNA library containing 2×10^5 clones was constructed using the primer-adaptor procedure (26) and the vector pSE-1 (27). The cloning strategy for the expression which was used has been previously described (17).

Preparation of human IL-13Rβ cDNA:

The RNA samples are copied with reverse transcriptase and subjected to PCR (polymerase chain reaction) using a sense primer corresponding to the sequence + 52 to + 71 and an antisense primer corresponding to + 489 to 470 (the numbering is made on the basis of the cDNA sequence shown in Figure 2). The PCR-amplified products are hybridized with a probe complementary to sequences + 445 to + 461 of the cDNA. The size markers are indicated on the left of the figure.

Isolation and analysis of the human IL-13Rα cDNA:

1) Preparation of the murine IL-13Rα probe

a) Culture of the B9 cells (28)

The B9 cells are cultured in RPMI medium (Gibco) supplemented with 10% foetal calf serum and 50 µg/ml of gentamycin.

b) Preparation of the RNA of the B9 cells.

The cells are washed twice with PBS buffer (phosphate buffered saline, reference 04104040-GIBCO-BRL). After centrifugation for 10 min at 1000 rpm, the cellular pellet is suspended in the lysis buffer of the following composition: 4M guanidine-thiocyanate; 25 mM sodium citrate pH 7; 0.5% sarcosyl; 0.1 M β2-mercapto-ethanol.

The suspension is sonicated using an Ultraturax sonicator No. 231256 (JANKE and KUNDEL) at the maximum power for one minute. Sodium acetate pH 4 is added to 0.2 M. The solution is extracted with one volume of a phenol/chloroform mixture (v/v:5/1).

The RNA contained in the aqueous phase is precipitated at -20°C with the aid of one volume of isopropanol. The pellet is resuspended in the lysis buffer. The solution is again extracted with a phenol/chloroform mixture and the RNA is precipitated with isopropanol. After washing the pellet with 70% and then 100% ethanol, the RNA is resuspended in water.

c) Preparation of the complementary DNA.

The cDNA is prepared from 5 µg of total RNA using a poly T12 primer. The total RNA is incubated in a volume of 30 µl of buffer: 50 mM Tris-HCl pH 8.3, 6 mM $MgCl_2$, 10 mM DTT, 40 mM KCl, containing 0.5 mM of each of the deoxynucleotide triphosphates and 30 units of Rnasin (Promega), for one hour at 37°C, and then for 10 minutes at 50°C, and then for a further 10 minutes at 37°C, with 200 units of the reverse transciptaze enzyme Rnase H (Gibco-BRL reference 8064A). The reaction is stopped by heating for 10 minutes at 65°C.

d) Specific amplification of a mouse IL-13Rα cDNA fragment by the PCR technique.

The polymerization is carried out with 6 µl of cDNA in 50 µl final volume with the buffer of the following composition: 10 mM Tris-HCl pH 8.3, 2.5 mM $MgCl_2$, 50 mM KCl, 4 dNTP 0.2 mM, 2 µg/ml of each of the two nucleic primers and 2.5 U of TAQ DNA polymerase (Beckman). The pairs of primers were chosen on the sequence published by Hilton (22).

Sense primer: nucleotide 249 to 268
5′ AGAGGAATTACCCCTGGATG 3′

Antisense primer: nucleotide 1256 to 1275
5′ TCAAGGAGCTGCTTTCTTCA 3′

The reaction is carried out for 30 cycles of 1 minute at 94°C, 1 minute at 58°C, 4 minutes at 72°C, followed by a final cycle of 10 minutes at 72°C.

e) Purification of the PCR amplification product.

After running on a 1% agarose gel (Sigma) in TAE buffer (40 mM, Tris-HCl, 1mM EDTA pH 7.9) for 1 hour at 100 volts, the gel is stained in the presence of 1µg/ml of ethidium bromide in the same buffer. The band corresponding to the amplification product (cDNA fragment of 1027 base pairs (bp) of IL-13Rα) is extracted using a Glass Max kit (Gibco).

f) Preparation of the probe.

25 ng of the purified cDNA fragment of 1027 bp corresponding to the mouse IL-13Rα receptor are labelled with phosphorus-32 with the BRL Random Primers DNA labelling systems kit at a specific activity of 2.4×10^9 dpm/µg; alternatively, 100 ng are labelled by nick translation using the Boeringher kit at a specific activity of 4×10^8 dpm/µg.

2) Isolation and analysis of the human IL-13Rα cDNA

a) Preparation of the total RNA

The total RNA was extracted from Caki-1 cells as described above in paragraph 1b.

b) Purification of the messenger RNA (polyA+ fraction).

The purification of the polyA+ fraction of the RNA is carried out using the DYNAL oligo $(dT)_{25}$ Dynabeads

kit (reference 610.05) following the procedure recommended by the manufacturer. The principle is based on the use of superparamagnetic polystyrene beads onto which a poly(dT)$_{25}$ oligonucleotide is attached. The polyA+ fraction is hybridized with the oligo(dT)$_{25}$ oligonucleotide coupled to the beads which are trapped on a magnetic support.

c) Northern blot.

5 µg of polyA+ messenger RNA are loaded on a 1% agarose, 8% formaldehyde denaturing gel in MOPS buffer (10mM pH 7.4, 0.5 mM EDTA). After migration and transfer onto an N+ Hybond membrane (Amersham) in a 20X SSC buffer, the RNA is fixed by heating in an oven at 80°C under vacuum. The membrane is then prehybridized for 2 hours at 42°C in the following buffer: 1 M NaCl, 30% formamide; 1% SDS, 5X Denhart's; 100 µg/ml of salmon sperm DNA. After 2 hours of prehybridization, the membrane is hybridized in the same buffer with a concentration of mouse IL-13Rα probe prepared by random priming of 2.5×10^6 dpm/ml, for 16 hours. The membrane is then washed twice for 30 minutes in 2X SSC buffer 0.1% SDS at room temperature for 2 hours at 50°C in the same buffer. After 4 days of exposure in a cassette (Molecular Dynamics), the Northern blot is analysed with an Instant Imager (Molecular Dynamics). A predominant transcript of 4200 bp and a doublet of 1500 bp and 2000 bp are detected in the Caki-1 cells, U373 and U937.

Characterization of the properties of the human IL-13Rα and IL-13Rβ:

The COS-7 or CHO cells are transfected in Petri dishes as described above (17). 24 hours later, the cells are trypsinized and cultured in 24-well plates at a density of 8×10^4 cells/well. After culturing for 48 hours at 37°C, the cells are used for the binding experiments (assays carried out in triplicate show a variation of less than 10%) with iodinated IL-13 as described (17). For the transfection, the COS-7 or CHO cells were transfected in 25-cm^2 plates using 0.6 mg of various

plasmids. After 24 hours, the cell monolayers are trypsinized and cultured in 12-well plates at 8×10^4 cells/well. Three days later, the binding and competition experiments are carried out with labelled IL-13 and with unlabelled IL-13 and/or IL-4. The results are representative of at least three experiments conducted independently.

Comparison of electrophoretic mobilities in EMSA of the nuclear extracts of the cells expressing the human IL-13Rα and/or IL-4R :

2×10^6 CHO cells are plated onto 10 cm Petri dishes. 24 hours later, the cells are transfected with 6 µg of plasmid DNA (34). After 48 hours, the cells are incubated at 37°C for 30 minutes in 3 ml of medium with or without IL-13 or IL-4 at a concentration of 100 ng per ml. The cells are then rinsed twice with a PBS-0.5 mM EDTA buffer and then harvested in 1.2 ml of PBS. The cells are then centrifuged and the cellular extracts prepared as described in (35). The EMSAs are then carried out as described in (36) with 10 to 20 µg of cellular extracts and with an oligonucleotide probe radiolabelled with ^{32}P (50,000-100,000 cpm), a probe corresponding to the Cε element of the human Cε promoter (37). The oligonucleotide probe synthesized has the following sequence:

5′-GATCCACTTCCCAAGAACAGA-3′.

EXAMPLES

EXAMPLE 1:

Analysis of the expression of human IL-13Rβ at the surface of Caki-1 cells

It was recently discovered that human renal carcinoma cells expressed, in addition to the receptors shared by IL-4 and IL-13, a large excess of specific IL-13 receptors (21). On the basis of these results, a sample of human carcinoma cell lines was studied for the attachment of IL-13 as described above (17). A specific line, Caki-1 (ATCC HTB46), which expresses a particularly large number of binding sites for IL-13, was analysed in greater detail. The Scatchard curves obtained from saturation experiments show the presence of binding sites with a Kd of 446±50 pM and a capacity of 7.2×10^4 receptors/cell (Figure 1a). In competition experiments, unlabelled IL-13 completely displaces labelled IL-13 in a dose-dependent manner, whereas IL-4 displaces with a high affinity about 10% of the labelled IL-13. Higher concentrations of IL-4 (greater than 100 nM) do not displace the remaining 90% of bound IL-13 (Figure 1b).

These results are in agreement with the existence of two sites, one shared by the two cytokines, the other specific for IL-13. The experiments on cross-linking by affinity for IL-13 show a complex of about 70 kDa, which coincides with the complex observed in similar cross-linking experiments with IL-13 in various cell types (17,21). Labelled IL-13 is completely displaced from the complex by IL-13 but not by IL-4, which is in agreement with the competition experiments (Figure 1c).

EXAMPLE 2:

Analysis of the secretion of IL-6 induced by IL-4 or IL-13.

The authors of the invention analysed the secretion induced by IL-4 or IL-13 on Caki-1 cells. The two cytokines induce the secretion of similar levels of IL-6, and the secretion is inhibited by antibodies specific for

the α chain of IL-4R and by the antagonist Y124DIL-4 (Figure 1d). This suggests that the receptors shared by the two cytokines in the Caki-1 cells are responsible for the induction of the secretion of IL-6. Similar results are observed when the phosphorylation of the protein complex IRS1/4PS (18) induced by IL-4 and IL-13 is analysed in the presence or in the absence of anti-IL-4R antibodies and of IL-4 antagonist.

These results, taken as a whole, suggest that the receptor complex IL-4/IL-13 expressed in the Caki cells is identical to that which was previously described and that the protein binding IL-13 (IL-13Rβ) which is over-expressed is a component of the receptor responsible for the recognition of IL-13 in a functional complex which includes IL-4R. These cells were therefore used as source of messenger RNA for the cloning of this IL-13 binding entity.

EXAMPLE 3:

Cloning of the primary subunit of the IL-13 receptor (IL-13Rβ)

The strategy for the cloning and expression which was used has been previously described (17). A cDNA library containing 2×10^5 recombinant clones was constructed (26) using Caki-1 cells. The library was divided into batches of 1000 cDNAs in which the DNA of each batch, in plasmid form, was introduced into COS-7 cells (29). The binding of labelled IL-13 to the transfected COS-7 cells makes it possible to identify the batches of clones encoding an IL-13 receptor. The positive batches were distributed out and rescreened until a single clone capable of carrying out the synthesis of a cell surface protein capable of binding IL-13 is identified. Two independent IL-13Rβ cDNAs were finally isolated. The complete nucleotide sequence of the IL-13Rβ cDNA and the amino acid sequence deduced therefrom are shown in Figure 2a. The cDNA has a length of 1298 bases excluding the poly-A tail and has a short 3′ untranslated region of 106 bases. A canonical AATAAA polyadenylation signal is *in*

the expected place. The open reading frame between nucleotides 53 and 1192 defines a polypeptide of 380 amino acids. The sequence encodes a membrane protein with a potential signal peptide, a single transmembrane domain and a short intracytoplasmic tail.

Four potential N-glycosylation sites are located in the extracelluar region. It is important to note that two consensus motifs considered as signatures of the type II family of cytokine receptors (30) are also present, the first being derived from an N-terminal disulphide bridge loop structure, the second being the WSXWS type motif located at the C-terminal end of the extracellular region. The very short cytoplasmic sequence might explain why it is only the receptor complex shared by IL-4 and by IL-13 in the Caki cells which transduces a signal in the cell.

Alignment studies demonstrate homologies with the human IL-5R α chain (51% similarity and 27% identity, Figure 2b) and, to a lesser extent, with the prolactin receptor. It is interesting to note that the IL-5R complex consists of an α chain which binds IL-5 but which needs another protein, the β chain shared with the IL-3 and GM-CSF receptors, to form a high-affinity receptor which is capable of transducing a signal (31).

EXAMPLE 4:

Detection of the human IL-13Rβ messenger RNAs in various cell lines

Surprisingly, in the Caki-1 cells, similar quantities of messenger RNAs for IL-13Rβ and IL-4R are detected by Northern analyses although a large excess of IL-13Rβ is expressed. This observation suggests that there is a greater translation of this mRNA compared with the IL-4R transcript and explains the lack of detection of the IL-13Rβ mRNA in the cell lines expressing a small number of IL-13 binding sites. RT-PCR analyses (Figure 3) show that the transcript found in the Caki-1 cells is also present at lower levels in the keratinocytic line A431, the premyeloid cells TF-1, the premocytic cells

U937 and the cell line B IM9. No transcript was detected in the Jurkat T cell line or in the pre-B NALM6 cell line. These results are in agreement with the IL-13 binding studies on these same lines previously described by the authors of the present invention (17), and with the known biological targets of IL-13.

EXAMPLE 5:

Binding analyses carried out on COS-7 cells transfected with human IL-13Rβ cDNA

The COS-7 cells transfected with the isolated cDNA encoding IL-13Rβ specifically bind labelled IL-13. The Scatchard analysis of the saturation curve shows a single component site with a Kd value of 250±30 pM and a maximum binding capacity of 5.6×10^5 receptors/cell (Figure 4a).

The affinity of the recombinant receptor is in good agreement with the Kd value of 446 pM for IL-13Rβ in the Caki-1 cells and for what has been described in several other cells (17). Consequently, in spite of a sequence homology with the α chain of IL-5R, the cloned receptor behaves differently since it does not need a second chain to reconstitute a high affinity binding site.

It is interesting to note that the protein binding IL-15 recently described likewise has the characteristic of binding IL-15 with a high affinity, in the absence of the other two components of the IL-15R complex (32).

In competition experiments, IL-13 is capable of inhibiting the binding of labelled IL-13 to the cloned receptor, with an inhibitory constant (Ki) of 1.5 ± 0.5 nM, whereas IL-4 does not inhibit the binding. The pharmacology of the cloned receptor is therefore similar to that of the IL-13Rβ present in Caki-1 cells. Cross-linking experiments show a radiolabelled band of 70 kDa. This band has the same mobility as that observed in the Caki cells as well as in other cells (17). This complex most probably corresponds to the 60-70 kDa band observed

in addition to the IL-4R 140 kDa band in cross-linking experiments carried out with labelled IL-4. This could also suggest that a strong interaction exists between the two proteins in the functional receptor complex. The authors of the present invention therefore checked if IL-13Rβ and IL-4R interact in the cell membrane to reconstitute a receptor which allows cross-competition between the two cytokines. The results of a coexpression experiment are shown in Figure 4 c and d.

It appears clearly that the expression of the two receptors, either separately or simultaneously, results in a large number of receptors which specifically recognize either of the two cytokines. However, when they are expressed together, a small number of receptors (5 to 10%) is capable of recognizing the two cytokines. The cotransfection of the γc chain with IL-4R and IL-13Rβ does not bring about an increase in the number of shared binding sites. These results suggest that the IL-13Rβ and IL-4R chains can interact with each other in the cell membrane to reconstitute a receptor for which IL-13 and IL-4 may be in competition. The low percentage of reconstituted receptors is an argument in favour of the presence of another protein (IL-13Rα) in limiting amounts in the COS cells which is necessary for the reconstitution of the receptor complex to which IL-13 and IL-4 bind competitively.

The results obtained in the transfection experiments with the γc chain demonstrate that this protein is not the limiting factor which was previously suggested (15). This conclusion is also supported by the absence of γc messenger RNA in the Caki-1 cells (21).

Another possible reason which explains the low number of reconstituted receptors is the existence of an incorrect stoichiometry of the two proteins in the cell membrane. However, cotransfections using different relative quantities of IL-4R and IL-13Rβ do not show a major difference in the number of reconstituted receptors. The possibility that another IL-13R with a greater capacity to interact with IL-4R exists was

confirmed in mice (22) and in man by the isolation of the IL-13Rα cDNA (cf. EXAMPLE 7). It should be noted that the expression of γc enhances the binding of IL-4 as previously described (19) but reduces the binding of IL-13, suggesting a complex interaction between the different chains.

EXAMPLE 6:

Study of the inhibition of the binding of IL-13 to its membrane receptor by a receptor in soluble form.

The results in transient expression (Figure 5) or on stable lines (Figure 6) are described.

The two cDNA sequences encoding IL-13Rβ and IL-13Rβs are inserted into the vector p7055 in place of the IL-2 cDNA (33). The resulting plasmids are called 2036 and 2034 respectively.

a) Transient expression

The CHO cells are inoculated into 12-well plates at 3×10^5 cells/well and transfected the next day by the DEAE-Dextran method as for the COS cells, either with the plasmid 2036 or 2034, or with the empty plasmid pSE-1 as control.

The cells are cultured for three days so as to allow accumulation of IL-13Rβs in the supernatant of the cells transfected with the plasmid 2034 and good expression of IL-13Rβ in the membrane of the cells transfected with the plasmid 2036.

The supernatant of the cells transfected with IL-13Rβs (2034) or the negative control (empty pSE-1) is then collected and the cells transfected with IL-13Rβ are used to study the inhibition of the binding of IL-13.

The binding of IL-13 to the surface of the CHO cells expressing IL-13Rβ (2036) is measured in the presence or otherwise of these crude supernatants diluted one half with the radioligand or in the presence of an excess of nonradiolabelled IL-13 (NSB). The binding is carried out on whole cells in a final volume of 500 ml with 300 pM of radioligand, in triplicate.

b) Stable lines

Two stable transformed CHO lines are obtained by transfection with the coding sequences of the complete IL-13Rβ (polypeptide of 380 residues) or of the IL-13Rβ in soluble form (IL-13Rβs, truncated polypeptide corresponding to residues 1 to 337 of IL-13Rβ). These sequences are inserted into the vector p7055.

The CHO-DHFR$^-$ cells are transfected with the plasmids 2036 (IL-13Rβ) and 2034 (IL-13Rβs) and the recombinant clones selected as previously described (33).

One of the clones CHO-IL-13Rβ (CHO 2036) obtained, having 2 to 5×10^5 sites per cell, is inoculated into a 12-well plate at a density of 10^5 cells per well and the cells are used two days later for binding experiments in the presence or otherwise of IL-13Rβs.

For that, the CHO-IL-13Rβs (CHO 2034) clones are inoculated into 6 cm dishes, in triplicate, at 5×10^5 cells per dish. After 3 days of accumulation in the culture medium, the medium (5 ml per dish) is collected for the IL-13 binding inhibition studies on IL-13Rβ of the CHO 2036 clone. In the same manner, the supernatant of CHO cells not expressing the soluble IL-13Rβ is collected.

The binding of IL-13 at the surface of the CHO 2036-22 clone is measured in the presence or otherwise of these crude supernatants diluted one half with the radioligand, or in the presence of an excess of nonradiolabelled IL-13 (NSB). The binding is carried out in triplicate, on whole cells, in a volume of 500 ml with 300 pM of radioligand.

The histograms of Figures 5 and 6 represent the inhibition of the binding of IL-13 on IL-13Rβ by IL-13Rβs. Inhibition of the binding of IL-13 to its receptor can be observed on several clones.

EXAMPLE 7

Cloning of the human IL-13Rα receptor

a) Preparation of the cDNA library from polyA+ messenger RNAs of Caki-1 cells.

Starting with 0.5 µg of polyA+ messenger RNA, single-stranded complementary DNA labelled with [^{32}P]dCTP (the complementary DNA obtained has a specific activity of 3000 dpm/ng) is prepared with the synthetic primer having the following sequence (comprising a BamHI site):

5'<GATCCGGGCCCTTTTTTTTTTTT <3'

in a volume of 30 µl of the following buffer: 50 mM Tris-HCl pH 8.3, 6mM $MgCl_2$, 10 mM DTT, 40 mM KCl, containing 0.5 mM of each of the deoxynucleic triphosphates, 30 µCi of [α^{32}P]dCTP and 30 U of Rnasin (Promega). After incubating for 1 hour at 37°C, and then for 10 minutes at 50°C and then for a further 10 minutes at 37°C, with 200 units of the reverse transcriptase enzyme Rnase H (Gibco -BRL), 4 µl of EDTA are added. The RNA template is then degraded by adding 6 µl of a 2 N NaOH solution and incubating for 5 minutes at 65°C.

To remove the synthetic primer, the complementary DNA is purified on a 1 ml Sephacryl S400 column (Pharmacia), equilibrated in TE buffer. The first two radioactive fractions are combined and precipitated with a 1/10 volume of a 10 M ammonium acetate solution and 2.5 volumes of ethanol, this after extraction with chloroform. The cDNA is then extended in 5' by adding a dG homopolymeric tail with 20 units of terminal transferase enzyme (Pharmacia 27073001). Next, incubation is performed in 20 µl of buffer having the following composition: 30 mM Tris-HCl pH 7.6: 1 mM cobalt chloride; 140 mM cacodylic acid; 0.1 mM DTT; 1 mM dGTP, for 15 minutes at 37°C, and then 2 µl of 0.5 M EDTA are added. A further treatment with sodium hydroxide is carried out without heating, followed by repurification on an S400 column, extraction with chloroform and precipitation with ethanol. The pellet is dissolved in 33 µl of TE buffer. The next stage consists in pairing the cloning vector pT7T3-18 through which a homopolymeric dC tail has been added beforehand after cutting with Pst1, the cDNA and the adaptor. The cDNA (33 µl) is brought into contact with 75 ng of vector pT7/T3-18 (5µl), 120 ng of adaptor (1µl) of the following sequence (comprising an Apa1

site),

5'AAAAAAAAAAAAAGGGCCCG 3'

10 µl of a 200 mM NaCl solution, and the mixture is incubated for 5 minutes at 65°C and then the reaction mixture is allowed to cool to room temperature. The next stage consists in ligating the cloning vector and the single-stranded cDNA in a reaction volume of 100 µl with 32.5 units of the enzyme T4 phage DNA ligase (Pharmacia) overnight at 15°C in a buffer having the composition: 50 mM Tris-HCl pH 7.5; 10 mM $MgCl_2$, 1 mM ATP. The proteins are then removed by extraction with phenol followed by extraction with chloroform and then a 1/10 volume of a 10 mM ammonium acetate solution and 2.5 volumes of ethanol are added. The mixture is centrifuged, the pellet is taken up in the buffer having the composition: 33 mM Tris-acetate pH 7.9, 62.5 mM potassium acetate, 1 mM magnesium acetate and 1 mM DTT; the second cDNA strand is synthesized in a volume of 30 µl with 30 units of the enzyme T4 phage DNA polymerase (Pharmacia) and a mixture of 1 mM of the four deoxynucleotide triphosphates as well as two units of the protein of the T4 phage gene 32 (Pharmacia) for one hour at 37°C. The mixture is extracted with phenol and traces are removed by depositing on a P10 column (Biogel P10-200-400 mesh - reference 15011050 - Biorad).

The last stage consists in transforming E. Coli MC 1061 cells by electroporation of the recombinant DNA using a Biorad Gene Pulser apparatus used at 2.5 kV under the conditions recommended by the manufacturer, and then the bacteria are cultured for one hour in LB medium having the composition:

bactotryptone 10 g/l; yeast extract 5 g/l; NaCl 10 g/l.

The number of independent clones obtained is determined by plating a 1/1000 dilution from the transformation after a one hour incubation on a dish of LB medium supplemented with 1.5% agar (w/v) and with 100 µg/ml of ampicillin called, in what follows, LB agar medium.

The number of independent clones obtained is 1

million.

b) Screening of the cDNA library.

The entire library was plated on agar medium (Petri dishes 150 mm in diameter) coated with Biodyne A membranes (PALL reference BNNG 132). After leaving overnight at 37°C, the clones are transferred by contact onto new membranes. The latter are treated by placing them on Wathman 3 MM paper impregnated with the following solutions: 0.5 N NaOH, 1.5 M NaCl for 5 minutes and then 0.5 M Tris-HCl pH 8, 1.5 M NaCl for 5 minutes. After treatment with proteinase K in the following buffer, 10 mM Tris-HCl pH8, 10 mM EDTA, 50 mM NaCl, 0.1% SDS, 100 µg/ml proteinase K for 30 minutes at 37°C, the membranes are thoroughly washed in 2X SSC buffer (sodium citrate-NaCl), and then dried in an oven under vacuum at 80°C for 20 minutes.

c) Prehybridization and hybridization of the membranes.

The membranes are then prehybridized for 2 hours at 42°C in the following buffer: 1 M NaCl; 30% formamide; 1% SDS; 5X Denhart's 100 µg/ml of salmon sperm DNA. After 2 hours of prehybridization, the membranes are hybridized in the same buffer with a concentration of mouse IL-13Rα probe prepared by nick translation of 2.5×10^6dpm/ml, for 16 hours. The membranes are washed for twice 30 minutes in 2X SSC, 0.1% SDS buffer at room temperature and then 2 hours at 50°C in the same buffer. After overnight exposure at -80°C in the presence of a Kodak X-OMAT film, several positive clones are detected.

d) Sequencing of a human IL-13Rα clone and analysis of the sequence.

The sequence is obtained using the Applied Biosystem kit (reference 401628). The complete nucleic sequence of the IL-13Rα cDNA and the amino acid sequence deduced therefrom are shown in Figure 7. The cDNA is 3999 bases long excluding the poly-A tail and has a long untranslated 3' region of 2145 bases.

A canonical polyadenylation signal exists at the expected place. The open reading frame between nucleotides 34 and 1851 defines a polypeptide of 427 amino acids. The sequence encodes a membrane protein with a potential signal peptide and a single transmembrane domain and a short intracytoplasmic region.

10 potential glycosylation sites are located in the extracelluar region. It is important to note that two consensus motifs considered as signatures of the type II family of cytokine receptors are also present, the first being derived from an N-terminal disulphide bridge loop structure, the second being the WSXWS type motif located at the C-terminal end of the extracelluar region.

EXAMPLE 8

Binding analyses carried out on COS-3 or CHO cells transfected with human IL-13Rα cDNA.

The CHO cells transfected with the isolated cDNA encoding IL-13Rα specifically bind labelled IL-13. The Scatchard analysis of the saturation curve shows a single component site with a Kd value of 4.5±0.4nM and a maximum binding capacity of 26000 receptors/cell (Figs. 8C and 8G).

The results of coexpression experiments are shown in Figures 8D and 8H.

Analysis of the results of Figure 8C shows that IL-13Rα is well expressed in the clone 2036 of the CHO cells. It can be noted that IL-4R displaces 60% of the binding of IL-13 in the CHO cells cotransfected with IL-4R and IL-13Rα cDNA (Figure 8H) but taking into account a Kd of 7.5 nM for IL-13Rα, there would be 10 times as many IL-13Rα sites as IL-4R sites.

The CHO-hIL4R cells (human IL-4R) expressing hIL-4R which are transfected with the cDNA encoding hIL-13Rα specifically bind labelled IL-13.

The Scatchard analysis of the saturation curve shows clearly 2 component sites, one of high affinity with a Kd value of 23±8.9 pM and a maximum binding capacity of 28000 sites/cell and the other of low affi-

nity with a Kd value of 4.2±1.4 nM and a maximum binding capacity of 150000 sites/cell (Fig. 8D).

The second site characterized has the same affinity as hIL-13Rα (human IL-13Rα) expressed alone and corresponds to the nonassociated IL-13Rα chains because they are expressed in a larger quantity than hIL-4R.

These high-affinity receptors reconstituted in the presence of the 2 hIL-13Rα and hIL-4R chains are capable of recognizing the 2 cytokines (Figs. 8D and 8H). This is even clearer on the COS/pSE1 cells coexpressing the 2 hIL-13Rα and hIL-4R chains in a comparable quantity where IL-4 displaces all the binding IL-13.

The affinity of the recombinant human IL-13Rα is comparable to that described for the mouse IL-13Rα receptor (2-10nM) (ref. 22).

In contrast to the hIL-13Rβ chain previously described, human IL-13Rα does not constitute, on its own, a high-affinity binding site.

IL-13Rα and IL-4R therefore interact in the cell membrane to reconstitute a high-affinity receptor.

EXAMPLE 9

Activation of the STAT proteins by IL-13 and IL-4 in the CHO cells coexpressing hIL-13Rα and hIL-4R.

In human PBMC cells, hIL-4 and IL-13 activate 2 tyrosine kinases of the janus family, Jak1 and Jak2 which phosphorylate a latent transcription factor, STAT6. This activated factor enters the nucleus and binds to specific elements in the promoters of the genes regulated by IL-4.

We chose the Cε element of the human Cε promoter as probe in an electrophoretic mobility switch assay (EMSA) to demonstrate the activation by IL-13 of a binding factor similar to STAT6.

The nuclear extracts of the CHO cells, expressing IL-13R alone, IL-4R alone, or the 2 chains together, stimulated with 100ng/ml of IL-13 or IL-4 for 30 min at 37°C, are incubated with the radiolabelled Cε element.

The nuclear extracts of the cells coexpressing hIL-13Rα and hIL-4R form a complex having the same mobil-

ity in EMSA whether the cells are induced with IL-4 or IL-13 (cf. Figure 9). On the other hand, with the cells expressing either chain alone, no complex is detected.

In the CHO cells expressing hIL-13Rα and hIL-4Rα, IL-13 and IL-4 therefore initiate the same signalling cascade.

The cloning of IL-13Rβ and IL-13Rα described here makes it possible to improve the knowledge of the factors involved in the responses specifically induced by IL-13 compared with the responses induced by IL-4. It makes it possible, in addition, to have a tool for studying the regulation of the expression of the receptor under normal and pathological conditions where IL-13 plays a key role.

Moreover, the availability of cDNA makes it possible to facilitate the cloning of other proteins necessary for the reconstitution of an Il-4/IL-13 receptor complex and is also useful for the manufacture or the rational modelling of new medicinal products capable of being specific antagonists of the activities of IL-13.

REFERENCES:

1. Minty, A. *et al.*, Nature, 1993, *362*, 248-250.
2. McKenzie, A.N. *et al.*, Proc. Natl. Acad. Sci. U.S.A, 1993, *90*, 3735-3739.
3. Defrance, T. *et al.*, J. Exp. Med., 1994, *179*, 135-143.
4. Punnonen, J. *et al.*, Proc. Natl. Acad.Sci. (USA), 1993, *90*, 3730-3734.
5. Fior, R. *et al.*, Eur. Cytokine Network, 1994, *5*, 593-600.
6. Muzio, M. R. F. *et al.*, Blood, 1994, 83, 1738-1743.
7. De Waal Malefyt, R. *et al.*, J. Immunol, 1993, *151*, 6370-6381.
8. Doyle, A. *et al.*, Eur. J. Immunol. 1994, *24*, 1441-1445.
9. Montaner, L.J. *et al.*, J. Exp. Med., 1993, *178*, 743-747.
10. Sozzani, P. *et al.*, J. Biol. Chem., 1995, *270*, 5084-5088.
11. Herbert, J.M. *et al.*, Febs Lett., 1993, *328*, 268-270.
12. Derocq, J.M. *et al.*, Febs Lett. 1994, *343*, 32-36.
13. Zurawski, G. *et al.*, Immunol. Today, 1994, *15*, 19-26.
14. Interleukin-13 for Cytokines in Health and Disease. Eds D.G. Remick and J.S. Frie, Marcel Decker, N.Y. 1996.
15. Zurawski S.M. *et al.*, Embo Journal, 1993, *12*, 2663-2670.
16. Aversa, G. *et al.*, J. Exp. Med., 1993, *178*, 2213-2218.
17. Vita, N. *et al.*, Biol. Chem., 1995, *270*, 3512-3517.
18. Lefort, S. *et al.*, Febs Lett., 1995, *366*, 122-126.
19. Kondo, M. *et al.*, Science, 1993, *262*, 1874-1883.
20. Russell, S.M. *et al.*, Science, 1993, *262*, 1880-1883.
21. Obiri, N. *et al.*, J. Biol. Chem., 1995, *270*, 8797-8804.
22. Hilton, D.J. *et al.*, Proc. Natl. Acad. Sci. USA,

1996, *93*, 497-501.

23. Callard, R.E. *et al.*, Immunology Today, 1996, *17*, 3 108-110.
24. Devereux, J. *et al.*, Nucleic Acids Res., 1984, *12*, 387-395.
25. Chomczynski, P. *et al.*, N. Anal. Biochem., 1987, *162*, 156-159.
26. Caput, D. *et al.*, Proc. Natl. Acad. Sci. USA, 1986, *83*, 1670-1674.
27. Minty, A. *et al.*, Eur. Cytokine Network, 1993, *4*, 99-110
28. Labit Le Bouteiller, C. *et al.*, J. of Immunol. Methods, 1995, *181*, 1, 29-36.
29. Seed, B. *et al.*, Proc. Natl. Acad. Sci. USA, 1987, *84*, 3365-3369.
30. Bazan, J.F. *et al.*, Proc. Natl. Acad. Sci. USA, 1990, *87*, 6934-6938.
31. Honjo, T. *et al.*, Current Opinion in Cell Biology, 1991, *1*, 201-203.
32. Giri, J.G. *et al.*, Embo Journal, 1993, *14*, 3654-3663.
33. Miloux, B. *et al.*, Gene, 1994, *149*, 341-344.
34. Sampayrac, L.M. *et al.*, PNAS USA, 1981, 78, 7575-7578.
35. Jiang, S-W *et al.*, Nucleic Acid Res., 1995, 23, 3607-3608.
36. Köhler, I. *et al.*, FEBS Letters, 1994, 345, 187-192.
37. Seidel, H.M. *et al.*, PNAS USA, 1995, 92, 3041-3045.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:
(A) NAME: SANOFI
(B) STREET: 32,34 rue MARBEUF
(C) CITY: PARIS
(E) COUNTRY: FRANCE
(F) POSTAL CODE (ZIP): 75374
(G) TELEPHONE: 0153774000
(H) TELEFAX: 0153774133

(ii) TITLE OF INVENTION: IL-13 receptor

(iii) NUMBER OF SEQUENCES: 4

(iv) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25 (EPO)

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1539 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens
(F) TISSUE TYPE: Carcinoma
(G) CELL TYPE: renal
(H) CELL LINE: caki-1

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

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TACAAGCTTT TGCACTTCAT CTTCAGACAC CGAGATAAAA GTTAACCCTC CTCAGGATTT 180

TGAGATAGTG GATTATGAAG AGAACCCGGA TACTTAGGTT ATCTCTATTT GCAATGGCAA 240

CCCCCACTGT CTCTGGATCA TTTTGTGTTG TGAAAGGAAT GCACAGTGGA ATATGAACTA 300

AAATACCGAA ACATTGGTAG TGAAACATGG AAGGCTAGTG TAGAGGTTAC CATCATTACT 360

AAGAATCTAC ATTACAAAGA TGGGTTTGAT CTTAACAAGG GCATTGAATT ATAGAAGGGC 420

GAAGATACAC ACGCTTTTAC CATGGCAATG CACAAATGGA TCAGAAGTTC AAAGTTCCAA 480

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CTGTTCTTGG AAACCTGGCA TAGGTTACAT TATGTCTGGG TACTTCTTGA TACCAATTAC 660

AACTTGTTTT ACTGGTATGA GGGCTTGGAT CATGCATTAA ATATATTTGG AAACAGTGTG 720

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(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 380 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens
(F) TISSUE TYPE: Carcinoma
(G) CELL TYPE: renal
(H) CELL LINE: Caki-1

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

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65 70 75 80

Trp Lys Thr Ile Ile Thr Lys Asn Leu His Tyr Lys Asp Gly Phe Asp
85 90 95

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Cys Thr Asn Gly Ser Glu Val Gln Ser Ser Trp Ala Glu Thr Thr Tyr
115 120 125

Trp Ile Ser Pro Gln Gly Ile Pro Glu Thr Lys Val Gln Asp Met Asp
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Cys Val Tyr Tyr Asn Trp Gln Tyr Leu Leu Cys Ser Trp Lys Pro Gly
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180 185 190

Gln Asn Ile Gly Cys Arg Phe Pro Tyr Leu Glu Ala Ser Asp Tyr Lys
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225 230 235 240

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Cys Phe Val Val Arg Ser Lys Val Asn Ile Tyr Cys Ser Asp Asp Gly
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325 330 335

Ser Lys Lys Thr Leu Leu Arg Phe Trp Leu Pro Phe Gly Phe Ile Leu
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(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4009 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens
(F) TISSUE TYPE: Carcinoma
(G) CELL TYPE: RENAL
(H) CELL LINE: Caki-1

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

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GCCTATGTGG ATTTTTTCCT AACATACCTA AGCAAACCCA GTGTCAGGAT GGTAATTCTT    3840
ATTCTTTCGT TCAGTTAAGT TTTTCCCTTC ATCTGGGCAC TGAAGGGATA TGTGAAACAA    3900
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(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 427 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens
(F) TISSUE TYPE: Carcinoma
(G) CELL TYPE: renal
(H) CELL LINE: Caki-1

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

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    50                  55                  60

Trp Tyr Phe Ser His Phe Gly Asp Lys Gln Asp Lys Lys Ile Ala Pro
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        115                 120                 125

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    130                 135                 140

Ser Trp Leu Pro Gly Arg Asn Thr Ser Pro Asp Thr Asn Tyr Thr Leu
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Asn Val Phe Tyr Val Gln Glu Ala Lys Cys Glu Asn Pro Glu Phe Glu
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Gly Lys Lys Arg Asn Ser Thr Leu Tyr Ile Thr Met Leu Leu Ile Val
            340                 345                 350

Pro Val Ile Val Ala Gly Ala Ile Ile Val Leu Leu Leu Tyr Leu Lys
        355                 360                 365

Arg Leu Lys Ile Ile Ile Phe Pro Pro Ile Pro Asp Pro Gly Lys Ile
    370                 375                 380

Phe Lys Glu Met Phe Gly Asp Gln Asn Asp Asp Thr Leu His Trp Lys
385                 390                 395                 400

Lys Tyr Asp Ile Tyr Glu Lys Gln Thr Lys Glu Glu Thr Asp Ser Val
                405                 410                 415

Val Leu Ile Glu Asn Leu Lys Lys Ala Ser Gln
            420                 425
```

CLAIMS

1. Purified polypeptide, comprising an amino acid sequence chosen from:

a) the sequence SEQ ID No. 2,

b) any biologically active sequence derived from SEQ ID No. 2.

2. Polypeptide according to Claim 1, characterized in that it comprises the amino acid sequence SEQ ID No. 2.

3. Polypeptide according to Claim 1, characterized in that it is a variant form of the polypeptide of sequence SEQ ID No. 2 in which the 8 C-terminal residues are substituted by the following 6 residues: VRCVTL.

4. Polypeptide according to Claim 1, characterized in that it is a soluble form stretching up to residue 343 and preferably up to residue 337.

5. Isolated nucleic acid sequence encoding a polypeptide according to any one of Claims 1 to 4.

6. Isolated nucleic acid sequence according to Claim 5, characterized in that it is chosen from:

a) the sequence SEQ ID No. 1,

b) the nucleic acid sequences capable of hybridizing to the sequence SEQ ID No. 1 and encoding a polypeptide having an IL-13 β receptor activity,

c) the nucleic acid sequences derived from the sequences a) and b) because of the degeneracy of the genetic code.

7. Nucleic acid sequence according to Claim 6, characterized in that it comprises or consists of the nucleotide linkage stretching from nucleotide No. 1 up to nucleotide 1081 and preferably up to nucleotide 1063 on the sequence SEQ ID No. 1.

8. Purified polypeptide, comprising an amino acid sequence chosen from:

a) the sequence SEQ ID No. 4,

b) any biologically active sequence derived from SEQ ID No. 4.

9. Polypeptide according to Claim 8, characterized

in that it comprises the amino acid sequence SEQ ID No. 4.

10. Polypeptide according to Claim 9, characterized in that it is a soluble form stretching up to residue 343 and preferably up to the residue between 336 and 342.

11. Isolated nucleic acid sequence encoding a polypeptide according to any one of Claims 8 to 10.

12. Isolated nucleic acid sequence according to Claim 11, characterized in that it is chosen from

a) the sequence SEQ ID No. 3,

b) the nucleic acid sequences capable of hybridizing to the sequence SEQ ID No. 3 and encoding a polypeptide having an IL-13 α receptor activity,

c) the nucleic acid sequences derived from the sequences a) and b) because of the degeneracy of the genetic code.

13. Nucleic acid sequence according to Claim 12, characterized in that it comprises or consists of the nucleotide linkage stretching from nucleotide No. 1 up to nucleotide 1059, and preferably up to nucleotides between numbers 1041 and 1056 on the sequence SEQ ID No. 3.

14. Cloning and/or expression vector containing a nucleic acid sequence according to any one of Claims 5 to 7 and 11 to 13.

15. Vector according to Claim 14, characterized in that it is the plasmid PSE-1.

16. Host cell transfected with a vector according to Claim 14 or 15.

17. Transfected host cell according to Claim 16, characterized in that it is a cell of the COS-7, COS-3 or CHO line.

18. Nucleotide probe characterized in that it hybridizes specifically with any one of the sequences according to Claims 5 to 7, their complementary sequences or the corresponding messenger RNAs.

19. Probe according to Claim 18, characterized in that it comprises at least 10 nucleotides.

20. Probe according to Claim 18, characterized in that it comprises the whole of the sequence SEQ ID No. 1

or its complementary strand.

21. Nucleotide probe, characterized in that it hybridizes specifically with any one of the sequences according to Claims 11 to 13, their complementary sequences or the corresponding messenger RNAs.

22. Probe according to Claim 21, characterized in that it comprises at least 10 nucleotides.

23. Nucleotide probe, characterized in that it comprises the whole of SEQ ID No. 3 or its complementary strand.

24. Antisense sequence capable of inhibiting, at least partially, the production of polypeptides according to any one of claims 1 to 4 and 8 to 10, characterized in that it is chosen from the sequences constituting the reading frame encoding a polypeptide according to any one of Claims 1 to 4 and 8 to 10 at the level of the transcript.

25. Use of a sequence according to any one of Claims 5 to 7 and 11 to 13, for the preparation of diagnostic nucleotide probes or of antisense sequences which can be used in gene therapy.

or its complementary strand.

21. Nucleotide probe, characterized in that it hybridizes specifically with any one of the sequences according to Claims 11 to 13, their complementary sequences or the corresponding messenger RNAs.

22. Probe according to Claim 21, characterized in that it comprises at least 10 nucleotides.

23. Nucleotide probe, characterized in that it comprises the whole of SEQ ID No. 3 or its complementary strand.

24. Antisense sequence capable of inhibiting, at least partially, the production of polypeptides according to any one of claims 1 to 4 and 8 to 10, characterized in that it is chosen from the sequences constituting the reading frame encoding a polypeptide according to any one of Claims 1 to 4 and 8 to 10 at the level of the transcript.

25. Use of a sequence according to any one of Claims 5 to 7 and 11 to 13, for the preparation of diagnostic nucleotide probes or of antisense sequences which can be used in gene therapy.

26. Use of a probe according to any one of Claims 18 to 23, as *IN VITRO* diagnostic tool for the detection, by hybridization, of the nucleic acid sequences encoding a polypeptide according to any one of Claims 1 to 4 or 8 to 10, in biological samples, or for revealing aberrant syntheses or genetic abnormalities such as the loss of heterozygosity or genetic rearrangement.

27. Use of a probe according to any one of Claims 18 to 23 for the detection of chromosomal abnormalities.

28. *IN VITRO* diagnostic method for the detection of aberrant syntheses or of genetic abnormalities at the level of the nucleic acid sequences encoding a polypeptide according to any one of Claims 1 to 4 or 8 to 10, characterized in that it comprises:

- bringing a nucleotide probe according to any one of Claims 19 to 23 into contact with a biological sample under conditions allowing the formation of a hybridization complex between the said probe and the above-

mentioned nucleotide sequence, optionally after a preliminary spell of amplification of the above-mentioned nucleotide sequence;

- detection of the hybridization complex which may be formed;
- optionally, sequencing the nucleotide sequence forming the hybridization complex with the probe of the invention.

29. Use of a nucleic acid sequence according to any one of Claims 5 to 7 and 11 to 13 for the production of a recombinant polypeptide according to any one of Claims 1 to 4 and 8 to 10.

30. Method for producing an IL-13 receptor recombinant polypeptide, characterized in that transfected cells according to Claim 16 or 17 are cultured under conditions allowing the expression of a recombinant polypeptide of sequence SEQ ID No. 2 or of sequence SEQ ID No. 4 or a derivative, and in that the said recombinant polypeptide is recovered.

31. Mono- or polyclonal antibodies, conjugated antibodies, or fragments thereof, characterized in that they are capable of specifically recognizing a polypeptide according to any one of Claims 1 to 4 and 8 to 10.

32. Use of antibodies according to the preceding claim, for the purification or detection of a polypeptide according to any one of Claims 1 to 4 and 8 to 10 in a biological sample.

33. Process for the *IN VITRO* diagnosis of pathologies correlated with an abnormal expression of IL-13 receptor in biological samples capable of containing the IL-13 receptor expressed at an abnormal level, characterized in that at least one antibody according to Claim 31 is brought into contact with the said biological sample, under conditions allowing the possible formation of specific immunological complexes between the IL-13 receptor and the said antibody(ies) and in that the specific immunological complexes which may be formed are detected.

34. Kit for the *IN VITRO* diagnosis of an abnormal expression of the IL-13 receptor in a biological sample and/or for measuring the level of expression of the IL-13 receptor in the said sample comprising:

- at least one antibody specific for the IL-13 receptor according to Claim 31, optionally attached onto a support,
- means for revealing the formation of specific antigen/antibody complexes between IL-13 receptor and the said antibody(ies) and/or means for quantifying these complexes.

35. Method for the identification and/or isolation of polypeptides according to Claim 1 or 8 or agents capable of modulating their activity, characterized in that a compound or a mixture containing various compounds, optionally nonidentified, is brought into contact with cells expressing at their surface a polypeptide according to Claim 1 or 8, under conditions allowing interaction between the polypeptide and the said compound, in the case where the latter would have an affinity for the polypeptide, and in that the compounds bound to the polypeptide, or those capable of modulating the biological activity thereof, are detected and/or isolated.

36. Ligand or modulator for a polypeptide as defined in Claims 1 to 4 or 8 to 10, capable of being obtained according to the method of Claim 35.

37. Pharmaceutical composition comprising, as active ingredient, a polypeptide according to any one of Claims 1 to 4 or 8 to 10.

38. Pharmaceutical composition according to the preceding claim, characterized in that it comprises a polypeptide according to Claim 4 or 10.

39. Use of a polypeptide according to any one of Claims 1 to 4, for screening agents capable of modulating the activity of IL-13Rβ.

40. Use of a polypeptide according to any one of Claims 8 to 10, for screening agents capable of modulating the activity of IL-13Rα.

41. Use of a polypeptide according to any one of

Claims 1 to 4, for the manufacture of products capable of modulating activity of IL-13Rβ.

42. Use of a polypeptide according to any one of Claims 8 to 10, for the manufacture of products capable of modulating the activity of IL-13Rα.

43. Use of a polypeptide according to Claim 4 or 10, for the synthesis of a medicinal product with IL-13 antagonizing effect.

SANOFI

IL - 13 RECEPTOR

ABSTRACT

This invention relates to a purified polypeptide, comprising an amino acid sequence chosen from:

a) the sequence SEQ ID No. 2,

b) any biologically active sequence derived from SEQ ID No. 2.

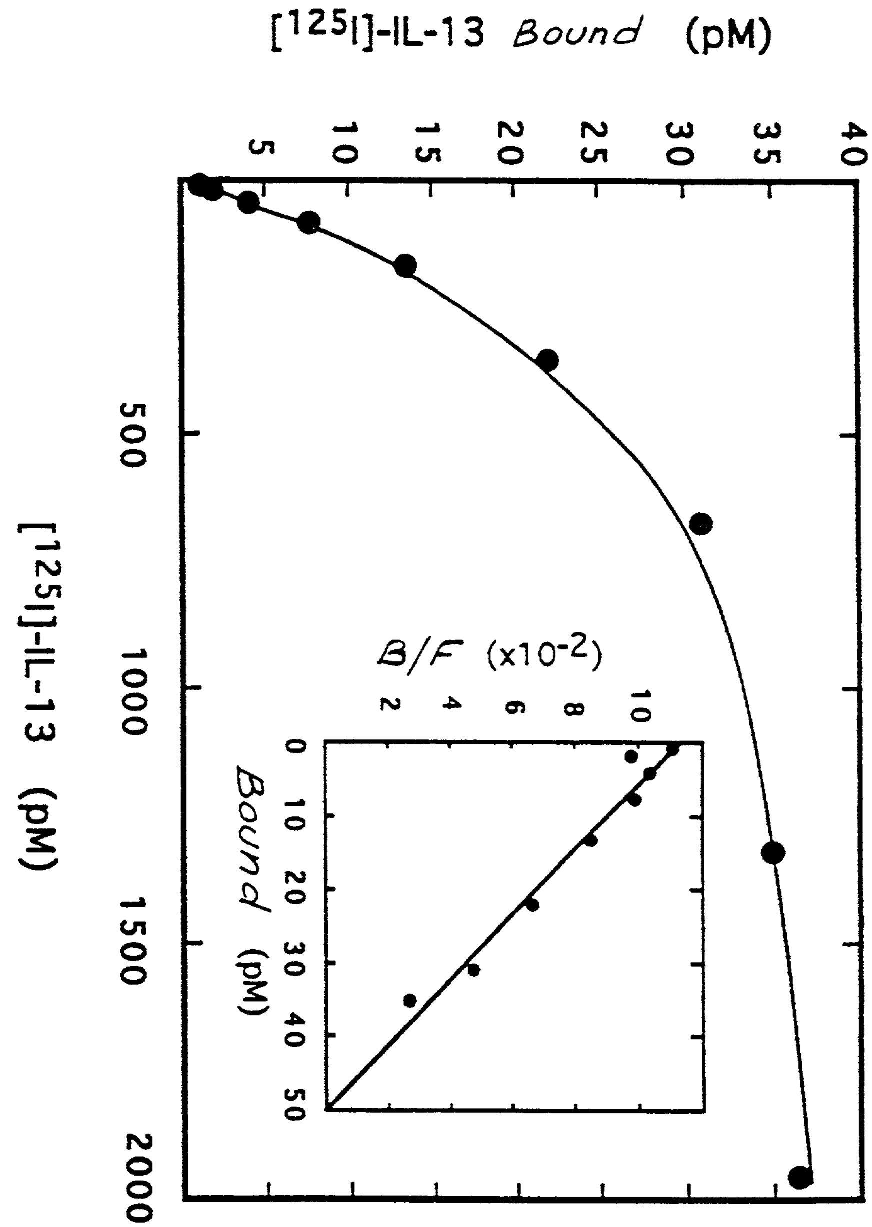


FIG. 1a

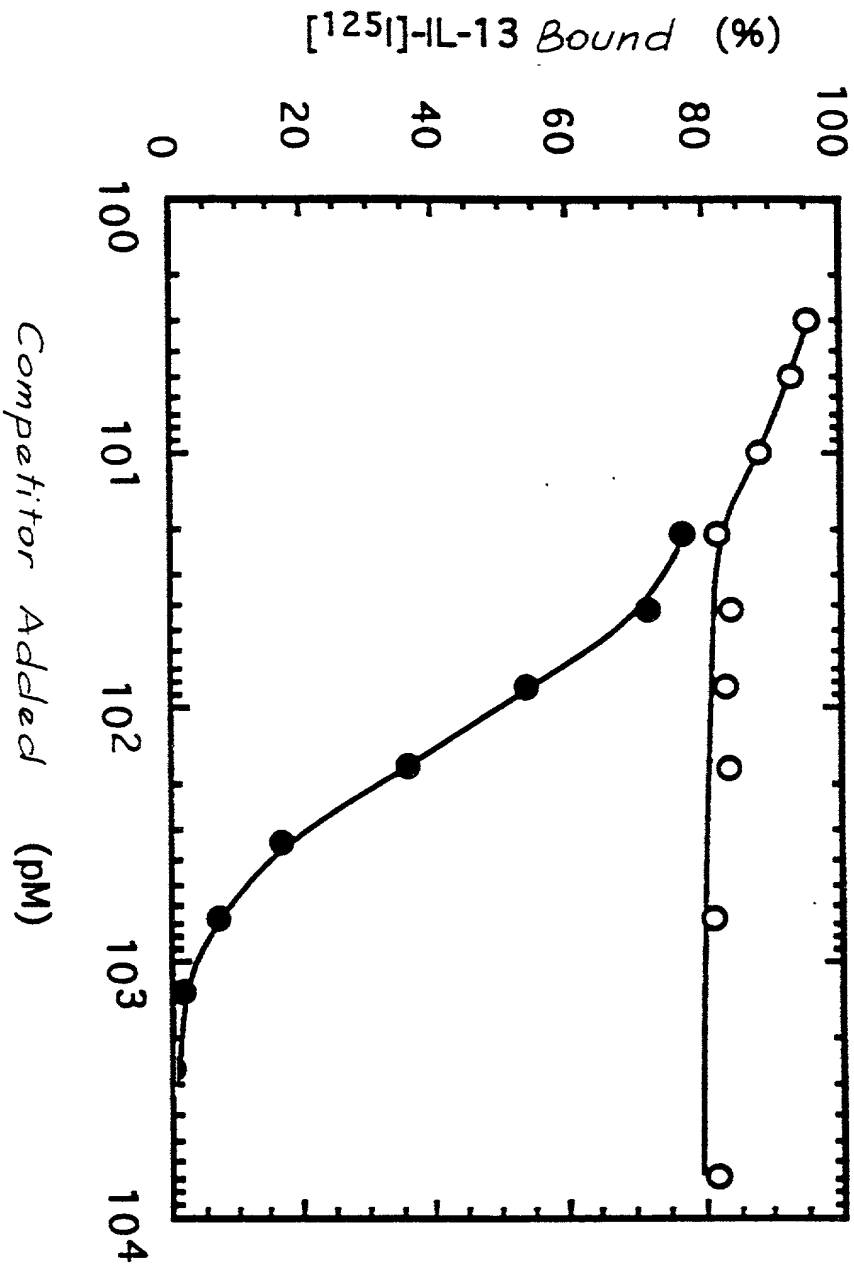


FIG.1b

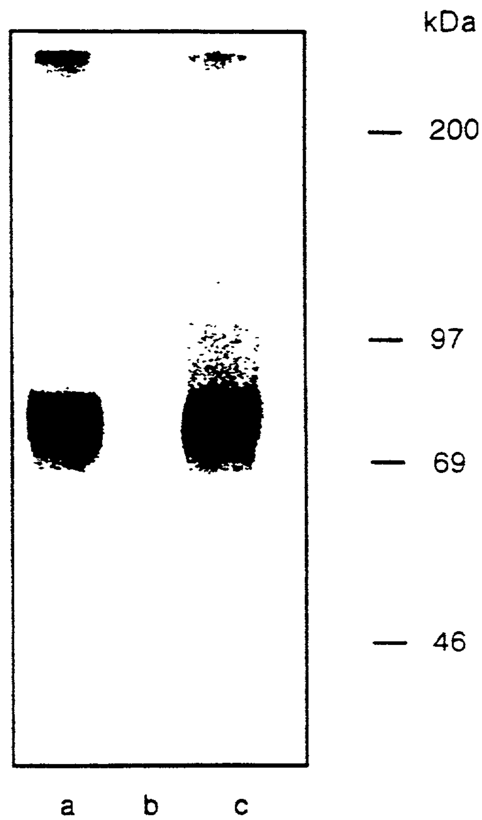


FIG.1c

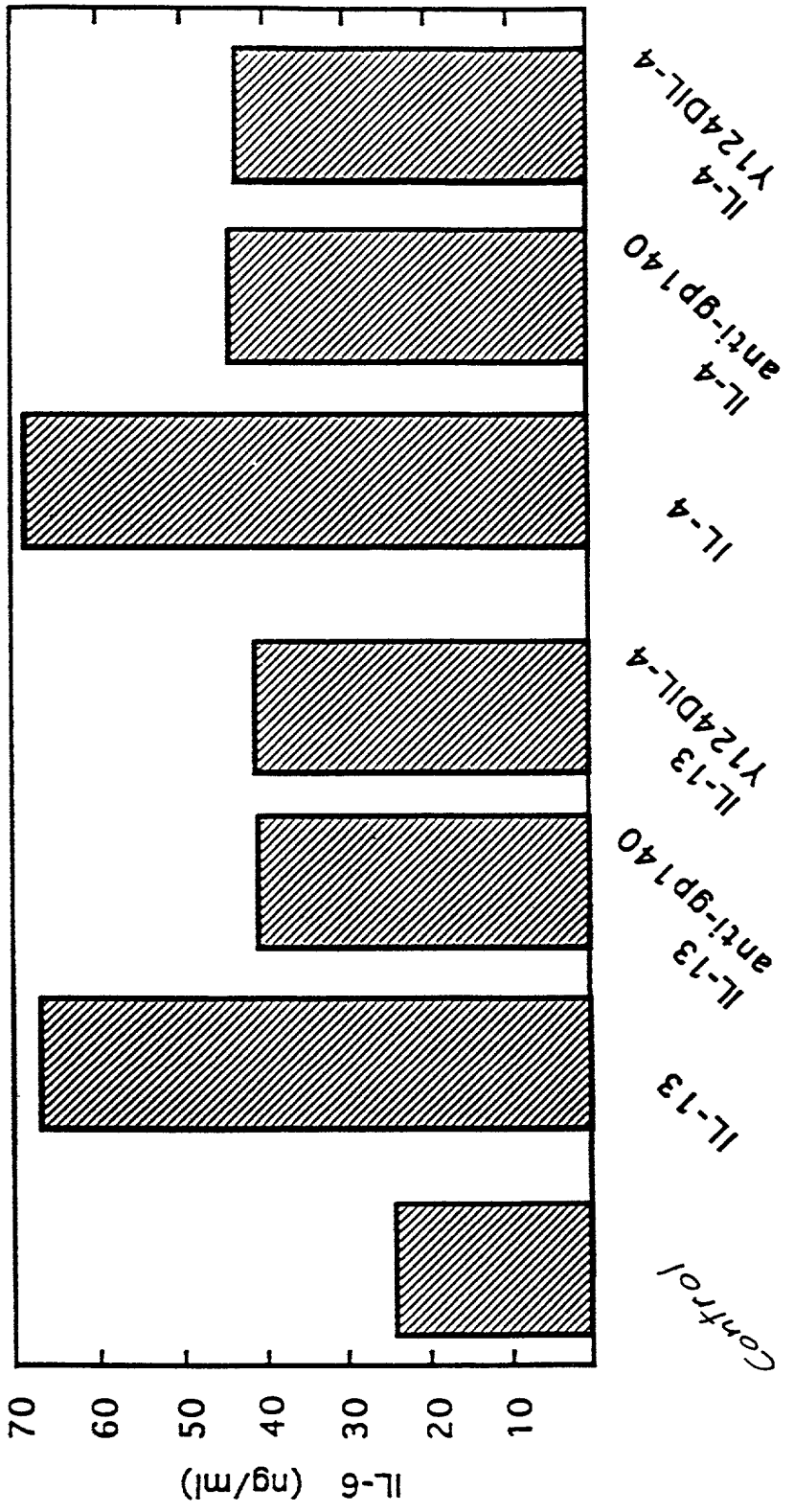


FIG.1d

```
  1   GGTGCCTGTCGGCGGGGAGAGAGGCAATATCAAGGTTTTAAATCTCGGAGAAATGGCT   58
  1                                                        MetAla    2

 59   TTCGTTTGCTTGGCTATCGGATGCTTATATACCTTTCTGATAAGCACAACATTTGGCTGT  118
  3   PheValCysLeuAlaIleGlyCysLeuTyrThrPheLeuIleSerThrThrPheGlyCys   22

119   ACTTCATCTTCAGACACCGAGATAAAAGTTAACCCTCCTCAGGATTTTGAGATAGTGGAT  178
 23   ThrSerSerSerAspThrGluIleLysValAsnProProGlnAspPheGluIleValAsp   42

179   CCCGGATACTTAGGTTATCTCTATTTGCAATGGCAACCCCCACTGTCTCTGGATCATTTT  238
 43   ProGlyTyrLeuGlyTyrLeuTyrLeuGlnTrpGlnProProLeuSerLeuAspHisPhe   62

239   AAGGAATGCACAGTGGAATATGAACTAAAATACCGAAACATTGGTAGTGAAACATGGAAG  298
 63   LysGluCysThrValGluTyrGluLeuLysTyrArgAsnIleGlySerGluThrTrpLys   82

299   ACCATCATTACTAAGAATCTACATTACAAAGATGGGTTTGATCTTAACAAGGGCATTGAA  358
 83   ThrIleIleThrLysAsnLeuHisTyrLysAspGlyPheAspLeuAsnLysGlyIleGlu  102

359   GCGAAGATACACACGCTTTTACCATGGCAATGCACAAATGGATCAGAAGTTCAAAGTTCC  418
103   AlaLysIleHisThrLeuLeuProTrpGlnCysThrAsnGlySerGluValGlnSerSer  122

419   TGGGCAGAAACTACTTATTGGATATCACCACAAGGAATTCCAGAAACTAAAGTTCAGGAT  478
123   TrpAlaGluThrThrTyrTrpIleSerProGlnGlyIleProGluThrLysValGlnAsp  142

479   ATGGATTGCGTATATTACAATTGGCAATATTTACTCTGTTCTTGGAAACCTGGCATAGGT  538
143   MetAspCysValTyrTyrAsnTrpGlnTyrLeuLeuCysSerTrpLysProGlyIleGly  162

539   GTACTTCTTGATACCAATTACAACTTGTTTTACTGGTATGAGGGCTTGGATCATGCATTA  598
163   ValLeuLeuAspThrAsnTyrAsnLeuPheTyrTrpTyrGluGlyLeuAspHisAlaLeu  182

599   CAGTGTGTTGATTACATCAAGGCTGATGGACAAAATATAGGATGCAGATTTCCCTATTTG  658
183   GlnCysValAspTyrIleLysAlaAspGlyGlnAsnIleGlyCysArgPheProTyrLeu  202
```

FIG.2a

```
659  GAGGCATCAGACTATAAAGATTTCTATATTTGTGTTAATGGATCATCAGAGAACAAGCCT  718
203  GluAlaSerAspTyrLysAspPheTyrIleCysValAsnGlySerSerGluAsnLysPro  222

719  ATCAGATCCAGTTATTTCACTTTTCAGCTTCAAAATATAGTTAAACCTTTGCCGCCAGTC  778
223  IleArgSerSerTyrPheThrPheGlnLeuGlnAsnIleValLysProLeuProProVal  242

779  TATCTTACTTTTACTCGGGAGAGTTCATGTGAAATTAAGCTGAAATGGAGCATACCTTTG  838
243  TyrLeuThrPheThrArgGluSerSerCysGluIleLysLeuLysTrpSerIleProLeu  262

839  GGACCTATTCCAGCAAGGTGTTTTGATTATGAAATTGAGATCAGAGAAGATGATACTACC  898
263  GlyProIleProAlaArgCysPheAspTyrGluIleGluIleArgGluAspAspThrThr  282

899  TTGGTGACTGCTACAGTTGAAAATGAAACATACACCTTGAAAACAACAAATGAAACCCGA  958
283  LeuValThrAlaThrValGluAsnGluThrTyrThrLeuLysThrThrAsnGluThrArg  302

959  CAATTATGCTTTGTAGTAAGAAGCAAAGTGAATATTTATTGCTCAGATGACGGAATTTGG  1018
303  GlnLeuCysPheValValArgSerLysValAsnIleTyrCysSerAspAspGlyIleTrp  322

1019 AGTGAGTGGAGTGATAAACAATGCTGGGAAGGTGAAGACCTATCGAAGAAAACTTTGCTA  1078
323  SerGluTrpSerAspLysGlnCysTrpGluGlyGluAspLeuSerLysLysThrLeuLeu  342

1079 CGTTTCTGGCTACCATTTGGTTTCATCTTAATATTAGTTATATTTGTAACCGGTCTGCTT  1138
343  ArgPheTrpLeuProPheGlyPheIleLeuIleLeuValIlePheValThrGlyLeuLeu  362

1139 TTGCGTAAGCCAAACACCTACCCAAAAATGATTCCAGAATTTTTCTGTGATACATGAAGA  1198
363  LeuArgLysProAsnThrTyrProLysMetIleProGluPhePheCysAspThr        381

1199 CTTTCCATATCAAGAGACATGGTATTGACTCAACAGTTTCCAGTCATGGCCAAATGTTCA  1258
1259 ATATGAGTCTCAATAAACTGAATTTTTCTTGCGAATGTTG  1298
```

FIG. 2a(continuation)

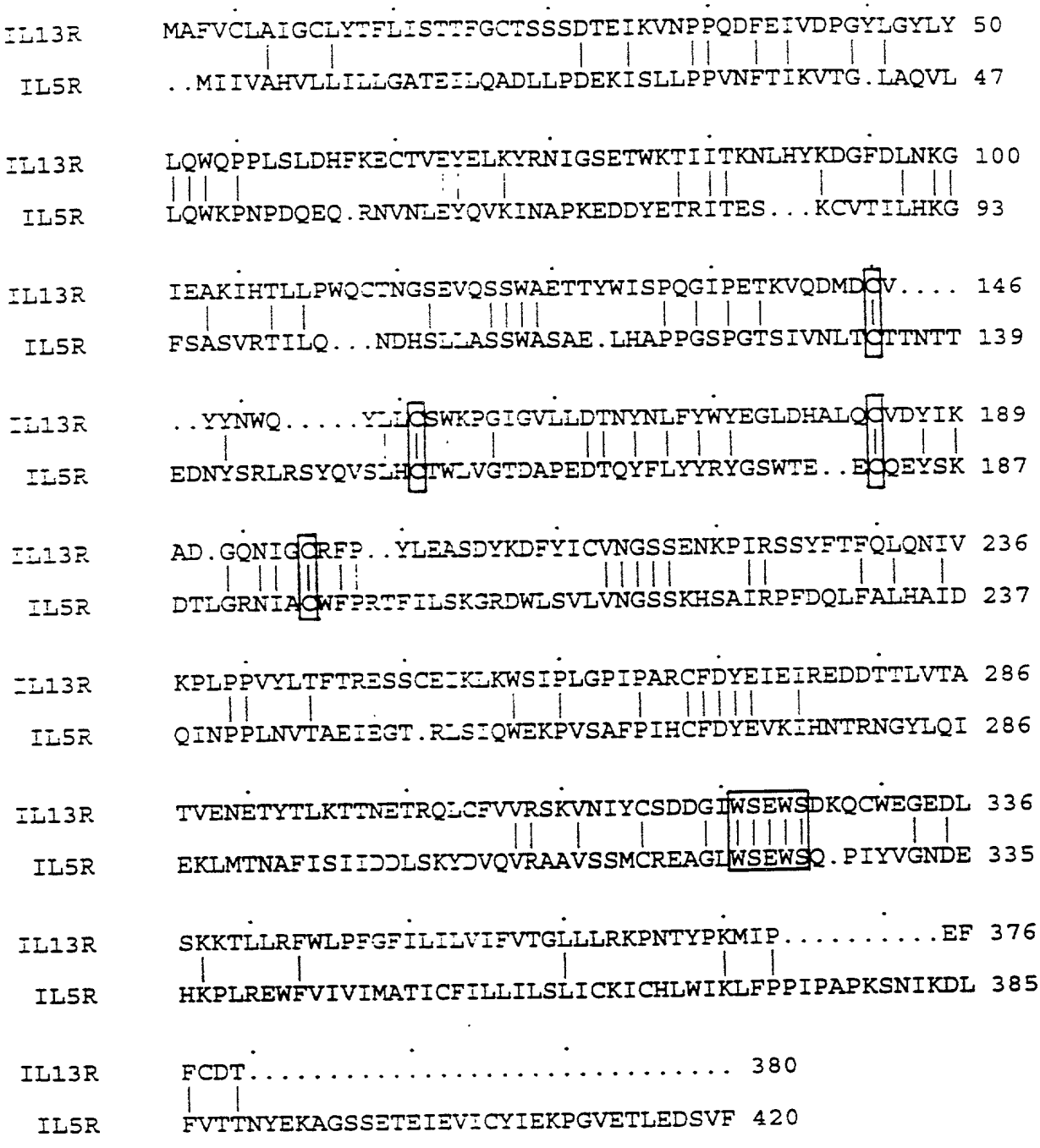


FIG. 2b

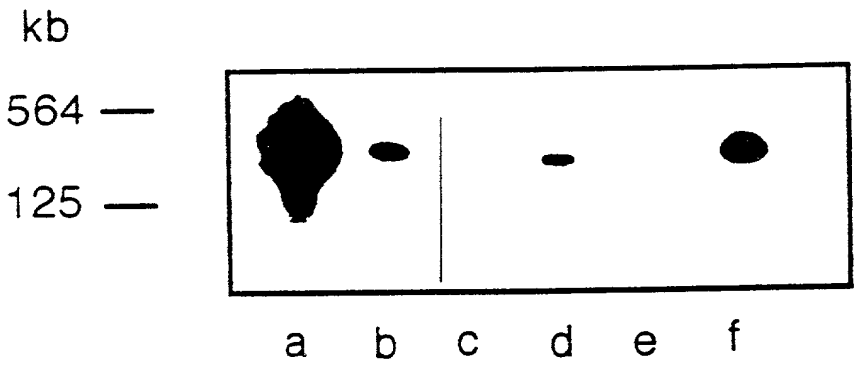


FIG.3

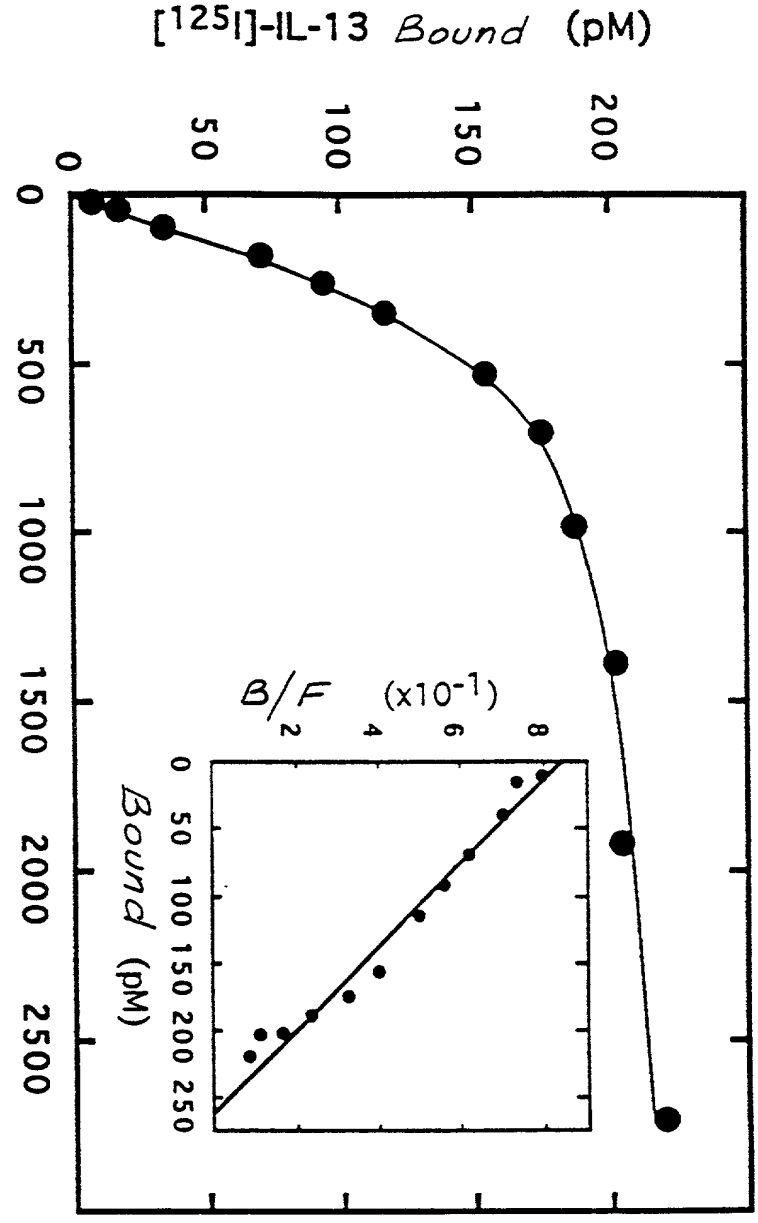


FIG.4a

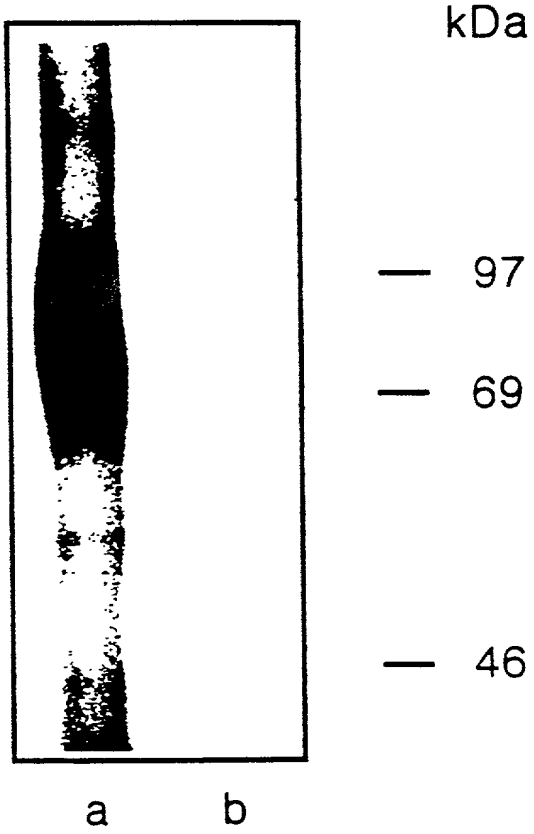


FIG.4b

FIG.4c

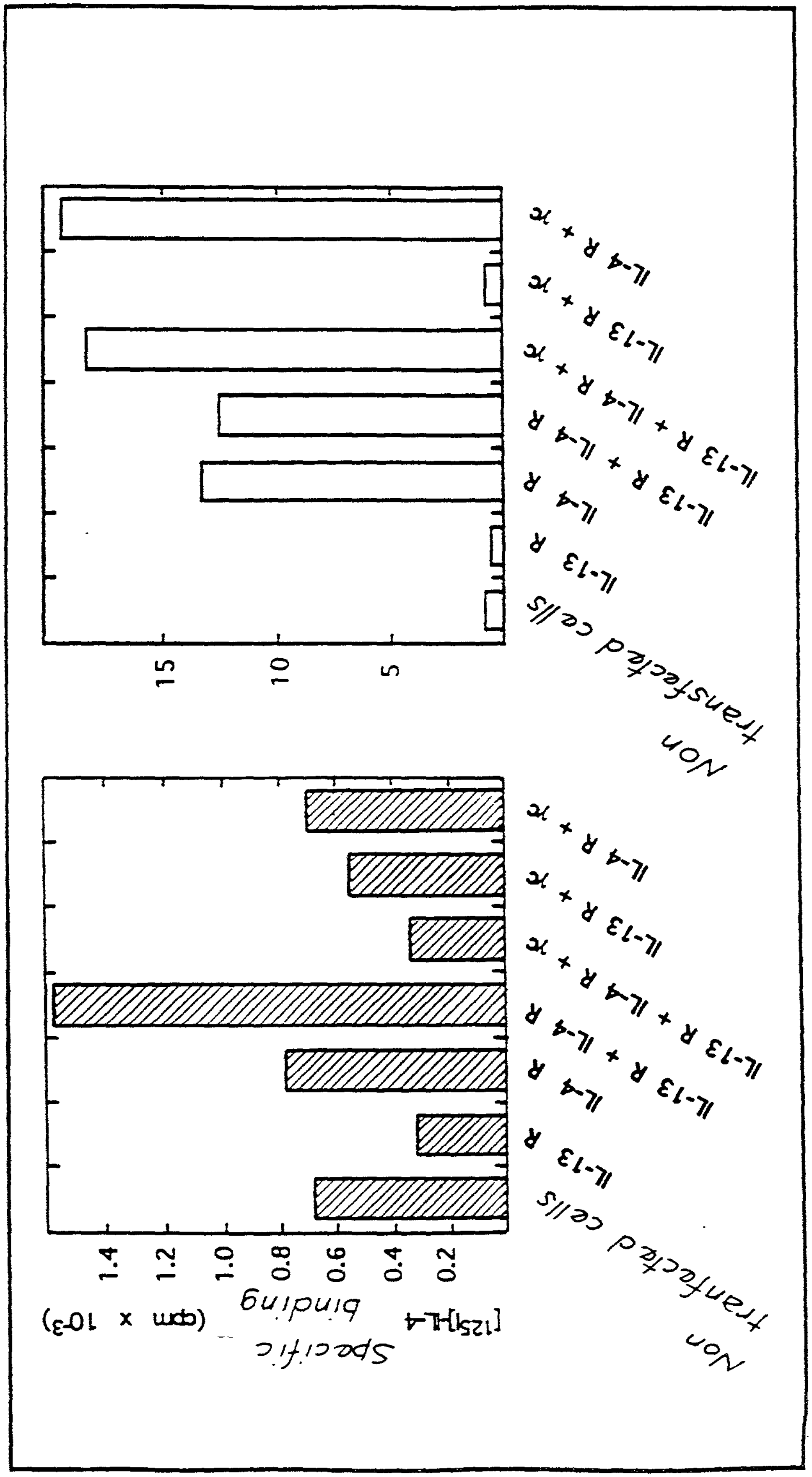

Specific [125]IL-4 binding (cpm x 10-3)
1.4
1.2
1.0
0.8
0.6
0.4
0.2
15
10
5
Non tranfected cells
IL-13 R
IL-4 R
IL-13 R + IL-4 R
IL-13 R + IL-4 R + γc
IL-13 R + γc
IL-4 R + γc
Non transfected cells

FIG.4d

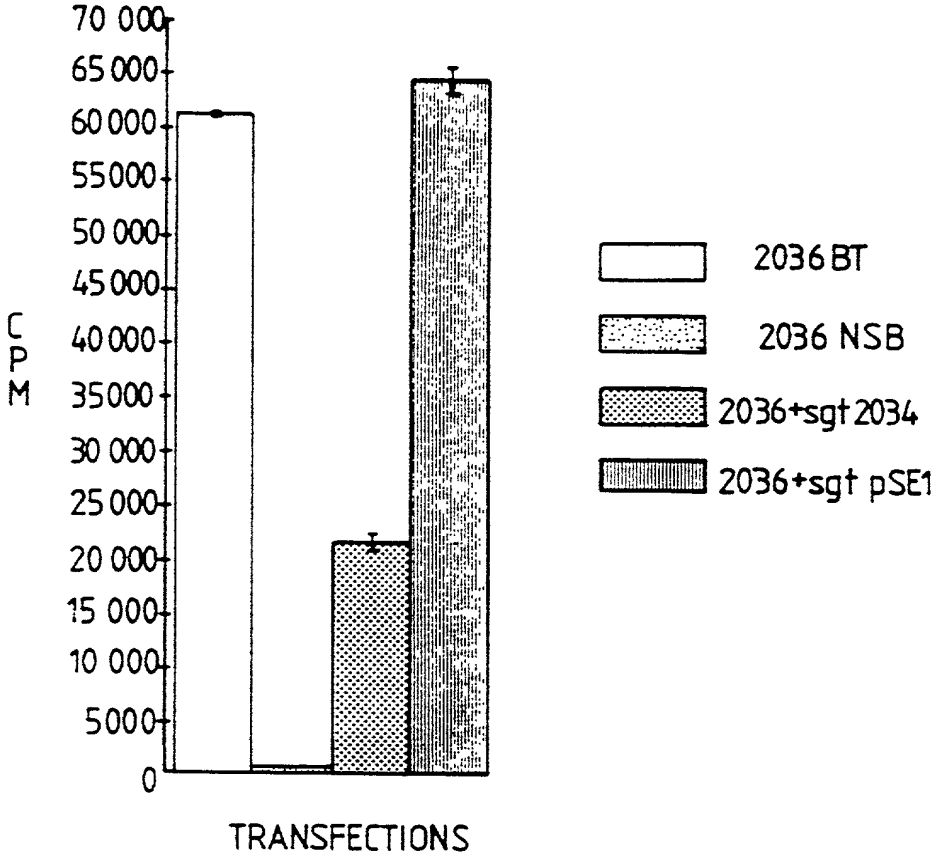
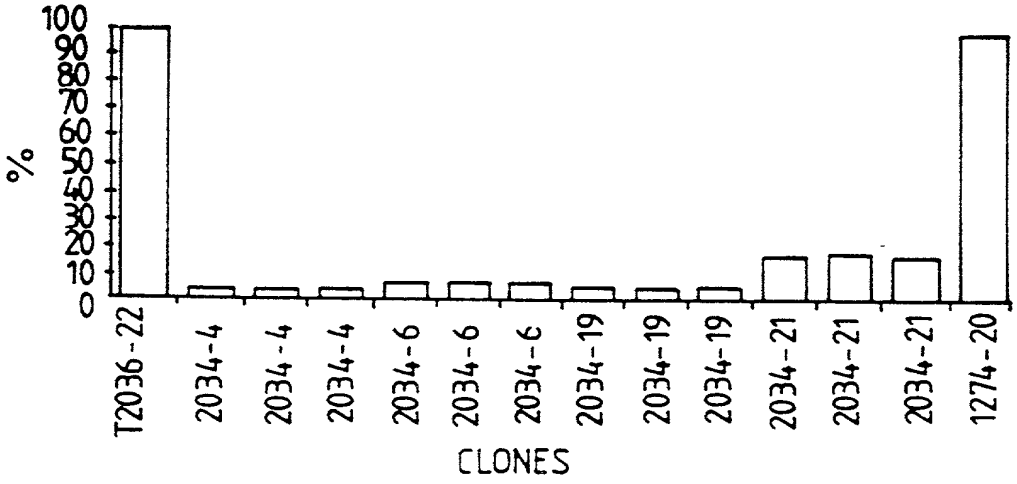

70 000
65 000
60 000
55000
50 000
45 000
40 000
35000
30 000
25 000
20 000
15 000
10 000
5000
0
CPM
TRANSFECTIONS
2036 BT
2036 NSB
2036+sgt 2034
2036+sgt pSE1

FIG. 5

FIG. 6


100
90
80
70
60
50
40
30
20
10
0
%
T2036-22
2034-4
2034-4
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2034-6
2034-6
2034-6
2034-19
2034-19
2034-19
2034-21
2034-21
2034-21
1274-20
CLONES

```
   1  TCAGCCCGGCCGGGCTCCGAGGCGAGAGGCTGCATGGAGTGGCCGGCGCGGCTCTGCGGG   60
 -10                                        M  E  W  P  A  R  L  C  G    9
  61  CTGTGGGCGCTGCTGCTCTGCGCCGGCGGCGGGGGCGGGGGCGGGGGCGCCGCGCCTACG  120
  10  L  W  A  L  L  L  C  A  G  G  G  G  G  G  G  G  A  A  P  T   29
 121  GAAACTCAGCCACCTGTGACAAATTTGAGTGTCTCTGTTGAAAACCTCTGCACAGTAATA  180
  30  E  T  Q  P  P  V  T [N  L  S  V] S  V  E  N  L  C  T  V  I   49
 181  TGGACATGGAATCCACCCGAGGGAGCCAGCTCAAATTGTAGTCTATGGTATTTTAGTCAT  240
  50  W  T  W  N  P  P  E  G  A  S  S [N  C  S  L] W  Y  F  S  H   69
 241  TTTGGCGACAAACAAGATAAGAAAATAGCTCCGGAAACTCGTCGTTCAATAGAAGTACCC  300
  70  F  G  D  K  Q  D  K  K  I  A  P  E  T  R  R  S  I  E  V  P   89
 301  CtGAATGAGAGGATTTGTCTGCAAGTGGGGTCCCAGTGTAGCACCAATGAGAGTGAGAAG  360
  90  L  N  E  R  I  C  L  Q  V  G  S  Q  C  S  T [N  E  S  E] K  109
 361  CCTAGCATTTTGGTTGAAAAATGCATCTCACCCCCAGAAGGTGATCCTGAGTCTGCTGTG  420
 110  P  S  I  L  V  E  K  C  I  S  P  P  E  G  D  P  E  S  A  V  129
 421  ACTGAGCTTCAATGCATTTGGCACAACCTGAGCTACATGAAGTGTTCTTGGCTCCCTGGA  480
 130  T  E  L  Q  C  I  W  H [N  L  S  Y] M  K  C  S  W  L  P  G  149
 481  AGGAATACCAGTCCCGACACTAACTATACTCTCTACTATTGGCACAGAAGCCTGGAAAAA  540
 150  R  N  T  S  P  D  T [N  Y  T  L] Y  Y  W  H  R  S  L  E  K  169
 541  ATTCATCAATGTGAAAACATCTTTAGAGAAGGCCAATACTTTGGTTGTTCCTTTGATCTG  600
 170  I  H  Q  C  E  N  I  F  R  E  G  Q  Y  F  G  C  S  F  D  L  189
 601  ACCAAAGTGAAGGATTCCAGTTTtGAACAACACAGTGTCCAAATAATGGTCAAGGATAAT  660
 190  T  K  V  K  D  S  S  F  E  Q  H  S  V  Q  I  M  V  K  D  N  209
 661  GCAGGAAAAATTAAACCATCCTTCAATATAGTGCCTTTAACTTCCCGTGTGAAACCTGAT  720
 210  A  G  K  I  K  P  S  F  N  I  V  P  L  T  S  R  V  K  P  D  229
 721  CCTCCACATATTAAAAACCTCTCCTTCCACAATGATGACCTATATGTGCAATGGGAGAAT  780
 230  P  P  H  I  K [N  L  S  F] H  N  D  D  L  Y  V  Q  W  E  N  249
 781  CCACAGAATTTTATTAGCAGATGCCTATTTTATGAAGTAGAAGTCAATAACAGCCAAACT  840
 250  P  Q  N  F  I  S  R  C  L  F  Y  E  V  E  V [N  N  S  Q] T  269
 841  GAGACACATAATGTTTTCTACGTCCAAGAGGCTAAATGTGAGAATCCAGAATTTGAGAGA  900
 270  E  T  H  N  V  F  Y  V  Q  E  A  K  C  E  N  P  E  F  E  R  289
 901  AATGTGGAGAATACATCTTGTTTCATGGTCCCTGGTGTTCTTCCTGATACTTTGAACACA  960
 290  N  V  E [N  T  S  C] F  M  V  P  G  V  L  P  D  T  L  N  T  309
 961  GTCAGAATAAGAGTCAAAACAAATAAGTTATGCTATGAGGATGACAAACTCTGGAGTAAT 1020
 310  V  R  I  R  V  K  T  N  K  L  C  Y  E  D  D  K  L  W  S [N  329
1021  TGGAGCCAAGAAATGAGTATAGGTAAGAAGCGCAATTCCACACTCTACATAACCATGTTA 1080
 330  W  S  Q] E  M  S  I  G  K  K  R [N  S  T  L] Y  I  T  M  L  349
1081  CTCATTGTTCCAGTCATCGTCGCAGGTGCAATCATAGTACTCCTGCTTTACCTAAAAAGG 1140
 350  L  I  V  P  V  I  V  A  G  A  I  I  V  L  L  L  Y  L  K  R  369
1141  CTCAAGATTATTATATTCCCTCCAATTCCTGATCCTGGCAAGATTTTTAAAGAAATGTTT 1200
 370  L  K  I  I  I  F  P  P  I  P  D  P  G  K  I  F  K  E  M  F  389
1201  GGAGACCAGAATGATGATACTCTGCACTGGAAGAAGTACGACATCTATGAGAAGCAAACC 1260
 390  G  D  Q  N  D  D  T  L  H  W  K  K  Y  D  I  Y  E  K  Q  T  409
1261  AAGGAGGAAACCGACTCTGTAGTGCTGATAGAAAACCTGAAGAAAGCCTCTCAGTGATGG 1320
 410  K  E  E  T  D  S  V  V  L  I  E  N  L  K  K  A  S  Q  *      429
```

FIG.7a

```
1381  TATCTGGGAACTTATTAAATGGAAACTGAAACTACTGCACCATTTAAAAACAGGCAGCTC   1440
1441  ATAAGAGCCACAGGTCTTTATGTTGAGTCGCGCACCGAAAAACTAAAAATAATGGGCGCT   1500
1501  TTGGAGAAGAGTGTGGAGTCATTCTCATTGAATTATAAAAGCCAGCAGGCTTCAAACTAG   1560
1561  GGGACAAAGCAAAAAGTGATGATAGTGGTGGAGTTAATCTTATCAAGAGTTGTGACAACT   1620
1621  TCCTGAGGGATCTATACTTGCTTTGTGTTCTTTGTGTCAACATGAACAAATTTTATTTGT   1680
1681  AGGGGAACTCATTTGGGGTGCAAATGCTAATGTCAAACTTGAGTCACAAAGAACATGTAG   1740
1741  AAAACAAAATGGATAAAATCTGATATGTATTGTTTGGGATCCTATTGAACCATGTTTGTG   1800
1801  GCTATTAAAACTCTTTTAACAGTCTGGGCTGGGTCCGGTGGCTCACGCCTGTAATCCCAG   1860
1861  CAATTTGGGAGTCCGAGGCGGGCGGATCACTCGAGGTCAGGAGTTCCAGACCAGCCTGAC   1920
1921  CAAAATGGTGAAACCTCCTCTCTACTAAAACTACAAAAATTAACTGGGTGTGGTGGCGCG   1980
1981  TGCCTGTAATCCCAGCTACTCGGGAAGCTGAGGCAGGTGAATTGTTTGAACCTGGGAGGT   2040
2041  GGAGGTTGCAGTGAGCAGAGATCACACCACTGCACTCTAGCCTGGGTGACAGAGCAAGAC   2100
2101  TCTGTCTAAAAAAACAAAACAAAACAAAACAAAACAAAAAAAACCTCTTAATATTCTGGAGT   2160
2161  CATCATTCCCTTCGACAGCATTTTCCTCTGCTTTGAAAGCCCCAGAAATCAGTGTTGGCC   2220
2221  ATGATGACAACTACAGAAAAACCAGAGGCAGCTTCTTTGCCAAGACCTTTCAAAGCCATT   2280
2281  TTAGGCTGTTAGGGGCAGTGGAGGTAgAATGACTCCTTGGGTATTAGAGTTTCAACCATG   2340
2341  AAGTCTCTAACAATGTaTTTTCTTCACCTCTGCTACTCAAGTAGCATTTACTGTGTCTTT   2400
2401  GGTTTGTGCTAGGCCCCCGGGTGTGAAGCACAGACCCCTTCCAGGGGTTTACAGTCTATt   2460
2461  TGAGACTCCTCAGTTCTTGCCACTTTTTTTTTTAATCTCCACCAGTCATTTTTCAGACCT   2520
2521  TTTAACTCCTCAATTCCAACACTGATTTCCCCTTTTGCATTCTCCCTCCTTCCCTTCCTT   2580
2581  GTAGCCTTTTGACTTTCATTGGAAATTAGGATGTAAATCTGCTCAGGAGACCTGGAGGAG   2640
2641  CAGAGGATAATTAGCATCTCAGGTTAAGTGTGAGTAATCTGAGAAACAATGACTAATTCT   2700
2701  TGCATATTTTGTAACTTCCATGTGAGGGTTTTCAGCATTGATATTTGTGCATTTTCTAAA   2760
2761  CAGAGATGAGGTGGTATCTTCACGTAGAACATTGGTATTCGCTTGAGAAAAAAAGAATAG   2820
2821  TTGAACCTATTTCTCTTTCTTTACAAGATGGGTCCAGGATTCCTCTTTTCTCTGCCATAA   2880
2881  ATGATTAATTAAATAGCTTTTGTGTCTTACATTGGTAGCCAGCCAGCCAAGGCTCTGTTT   2940
2941  ATGCTTTTGGGGGGCATATATTGGGTTCCATTCTCACCTATCCACACAACATATCCGTAT   3000
3001  ATATCCCCTCTACTCTTACTTCCCCCAAATTTAAAGAAGTATGGGAAATGAGAGGCATTT   3060
3061  CCCCCACCCCATTTCTCTCCTCACACACAGACTCATATTACTGGTAGGAACTTGAGAACT   3120
3121  TTATTTCCAAGTTGTTCAAACATTTACCAATCATATTAATACAATGATGCTATTTGCAAT   3180
3181  TCCTGCTCCTAGGGGAGGGGAGATAAGAAACCCTCACTCTCTACAGGTTTGGGTACAAGT   3240
3241  GGCAACCTGCTTCCATGGCCGTGTAGAAGCATGGTGCCCTGGCTTCTCTGAGGAAGCTGG   3300
3301  GGTTCATGACAATGGCAGATGTAAAGTTATTCTTGAAGTCAGATTGAGGCTGGGAGACAG   3360
3361  CCGTAGTAGATGTTCTACTTTGTTCTGCTGTTCTCTAGAAAGAATATTTGGTTTTCCTGT   3420
3421  ATAGGAATGAGATTAATTCCTTTCCAGGTATTTTATAATTCTGGGAAGCAAAACCCATGC   3480
3481  CTCCCCCTAGCCATTTTTACTGTTATCCTATTTAGATGGCCATGAAGAGGATGCTGTGAA   3540
3541  ATTCCCAACAAACATTGATGCTGACAGTCATGCAGTCTGGGAGTGGGGAAGTGATCTTTT   3600
3601  GTTCCCATCCTCTTCTTTTAGCAGTAAAATAGCTGAGGGAAAAGGGAGGGAAAAGGAAGT   3660
3661  TATGGGAATACCTGTGGTGGTTGTGATCCCTAGGTCTTGGGAGCTCTTGGAGGTGTCTGT   3720
3721  ATCAGTGGATTTCCCATCCCCTGTGGGAAATTAGTAGGCTCATTTACTGTTTTAGGTCTA   3780
3781  GCCTATGTGGATTTTTTCCTAACATACCTAAGCAAACCCAGTGTCAGGATGGTAATTCTT   3840
3841  ATTCTTTCGTTCAGTTAAGTTTTTCCCTTCATCTGGGCACTGAAGGGATATGTGAAACAA   3900
3901  TGTTAACATTTTTGGTAGTCTTCAACCAGGGATTGTTTCTGTTTAACTTCTTATAGGAAA   3960
3961  GCTTGAGTAAAATAAATATTGTCTTTTTGTATGTCACCCaaaaaaaaaa  4009
```

FIG. 7a (continuation)

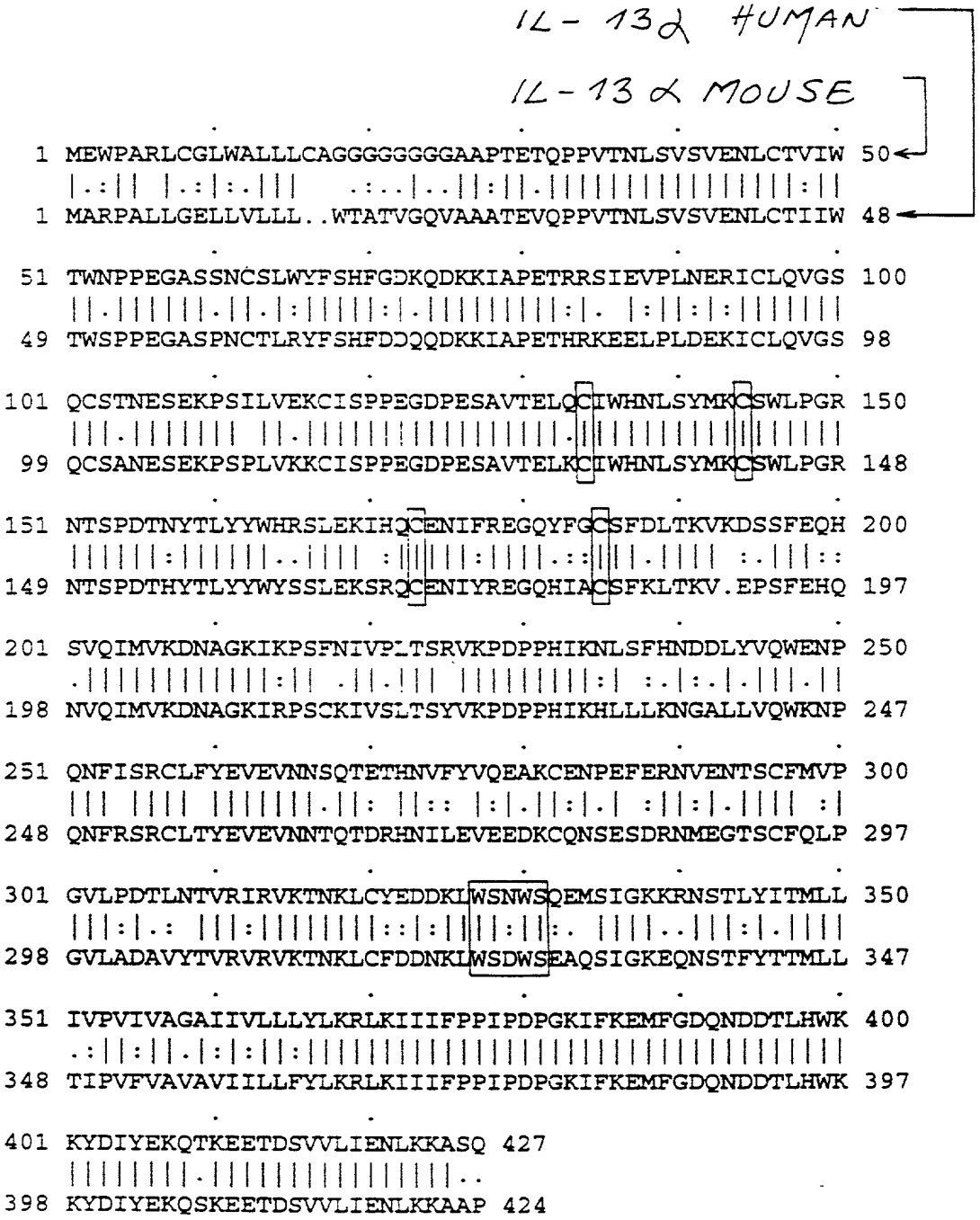

IL-13α HUMAN
IL-13α MOUSE
1 MEWPARLCGLWALLLCAGGGGGGGGAAPTETQPPVTNLSVSVENLCTVIW 50
1 MARPALLGELLVLLL..WTATVGQVAAATEVQPPVTNLSVSVENLCTIIW 48
51 TWNPPEGASSNCSLWYFSHFGDKQDKKIAPETRRSIEVPLNERICLQVGS 100
49 TWSPPEGASPNCTLRYFSHFDDQQDKKIAPETHRKEELPLDEKICLQVGS 98
101 QCSTNESEKPSILVEKCISPPEGDPESAVTELQCIWHNLSYMKCSWLPGR 150
99 QCSANESEKPSPLVKKCISPPEGDPESAVTELKCIWHNLSYMKCSWLPGR 148
151 NTSPDTNYTLYYWHRSLEKIHQCENIFREGQYFGCSFDLTKVKDSSFEQH 200
149 NTSPDTHYTLYYWYSSLEKSRQCENIYREGQHIACSFKLTKV.EPSFEHQ 197
201 SVQIMVKDNAGKIKPSFNIVPLTSRVKPDPPHIKNLSFHNDDLYVQWENP 250
198 NVQIMVKDNAGKIRPSCKIVSLTSYVKPDPPHIKHLLLLKNGALLVQWKNP 247
251 QNFISRCLFYEVEVNNSQTETHNVFYVQEAKCENPEFERNVENTSCFMVP 300
248 QNFRSRCLTYEVEVNNTQTDRHNILEVEEDKCQNSESDRNMEGTSCFQLP 297
301 GVLPDTLNTVRIRVKTNKLCYEDDKLWSNWSQEMSIGKKRNSTLYITMLL 350
298 GVLADAVYTVRVRVKTNKLCFDDNKLWSDWSEAQSIGKEQNSTFYTTMLL 347
351 IVPVIVAGAIIVLLLYLKRLKIIIFPPIPDPGKIFKEMFGDQNDDTLHWK 400
348 TIPVFVAVAVIILLFYLKRLKIIIFPPIPDPGKIFKEMFGDQNDDTLHWK 397
401 KYDIYEKQTKEETDSVVLIENLKKASQ 427
398 KYDIYEKQSKEETDSVVLIENLKKAAP 424

FIG. 7b

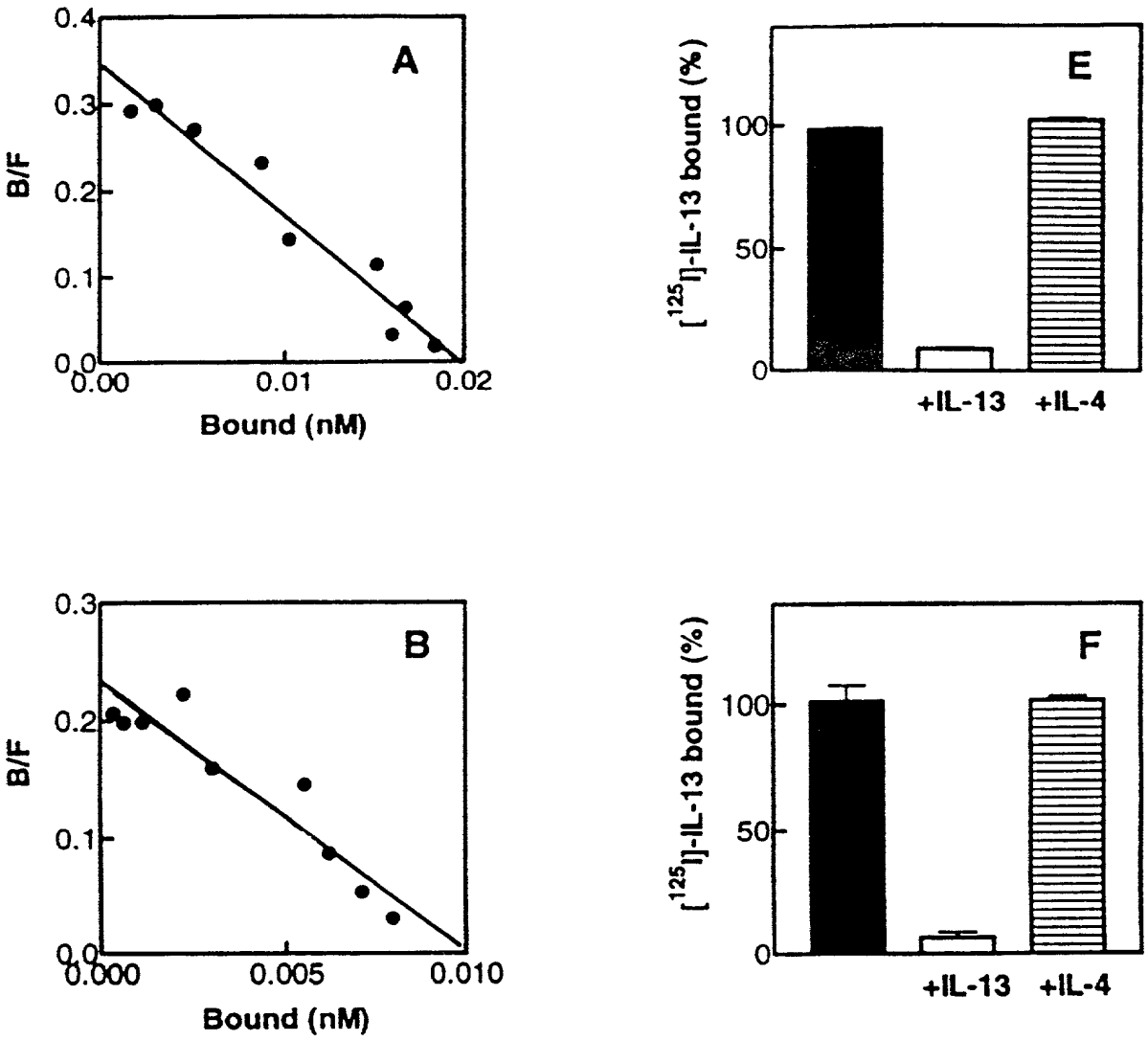
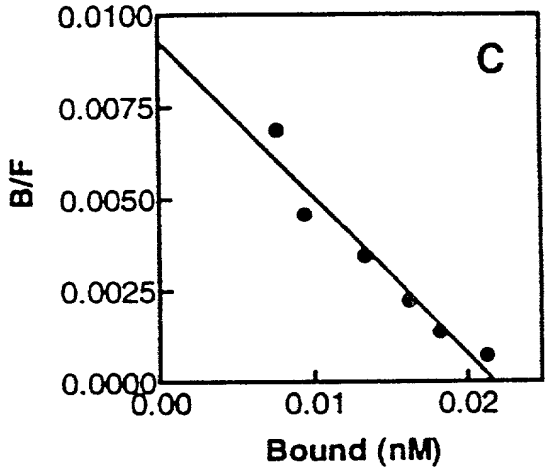
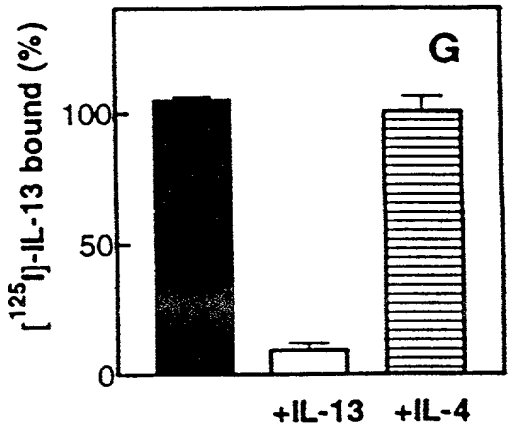
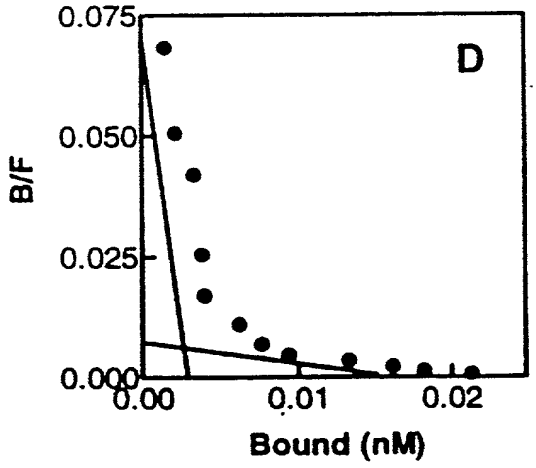

A
B/F
Bound (nM)
0.4
0.3
0.2
0.1
0.0
0.00
0.01
0.02
B
0.3
0.2
0.1
0.0
0.000
0.005
0.010
E
F
[125I]-IL-13 bound (%)
100
50
0
+IL-13
+IL-4

FIG.8







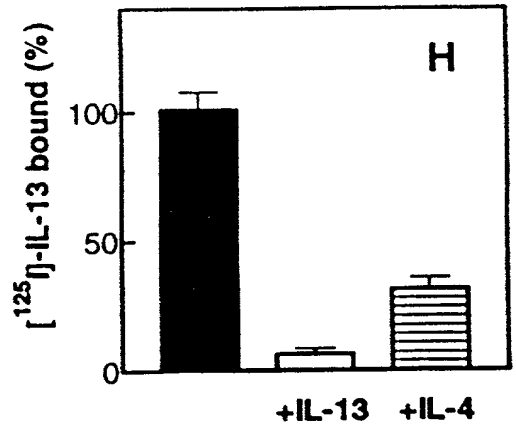


FIG. 8 (continuation)

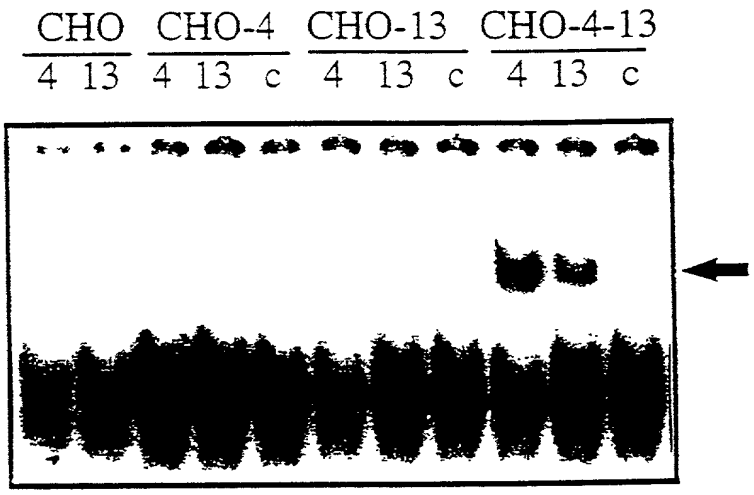
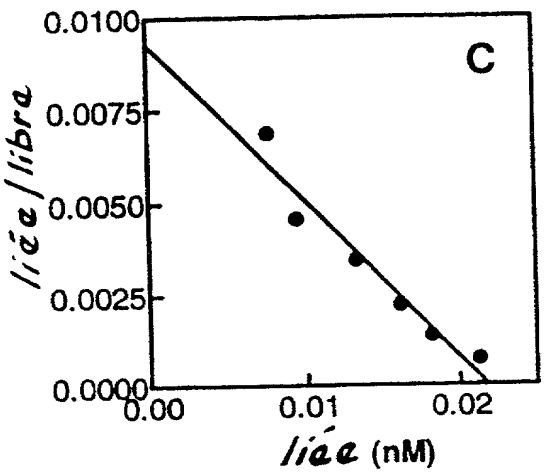
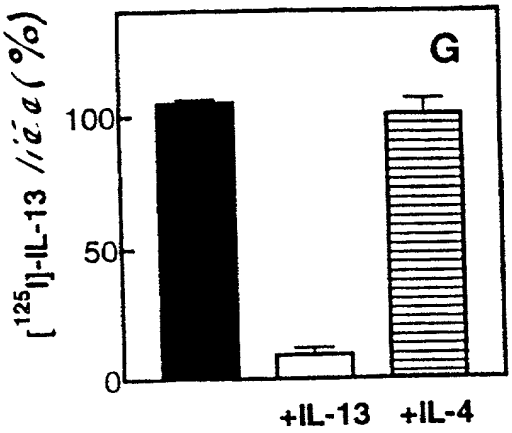
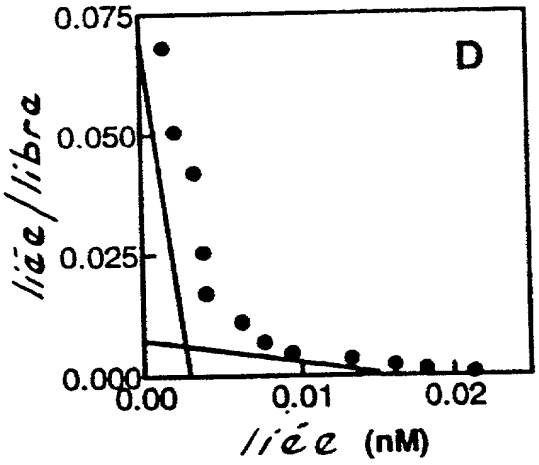


FIG.9


C
0.0100
0.0075
0.0050
0.0025
0.0000
0.00
0.01
0.02
liée/libre
liée (nM)


G
100
50
0
[125I]-IL-13 liée (%)
+IL-13
+IL-4


D
0.075
0.050
0.025
0.000
0.00
0.01
0.02
liée/libre
liée (nM)

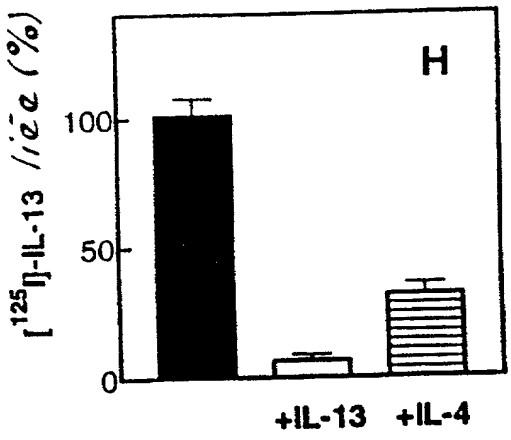

H
100
50
0
[125I]-IL-13 liée (%)
+IL-13
+IL-4

FIG.8 (suite)

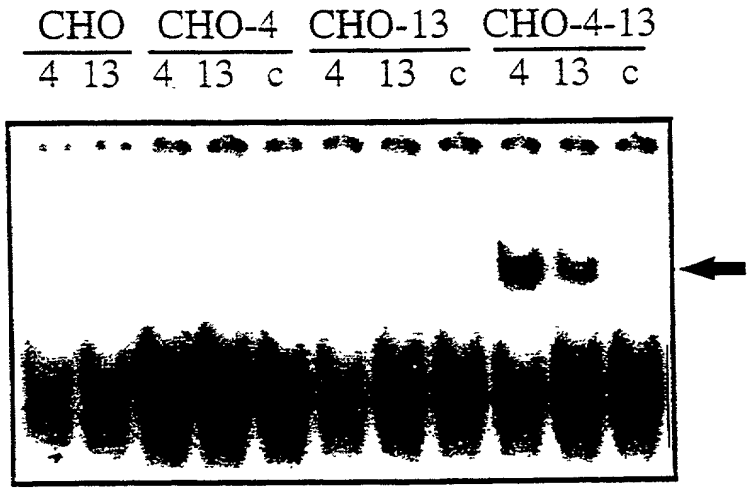


FIG.9

14 SEP 1998 IVD 924

#4

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of: Caput et al.

Serial No.: 09/077,817

Filed: 06/10/98

Group Art Unit: Unknown

For: IL-13 Receptors

CERTIFICATE UNDER 37 C.F.R. 1.8(a)

I hereby certify that this correspondence is being deposited on the date indicated below with the United States Postal Service as first class mail addressed to: Assistant Commissioner for Patents, Attn: Application Processing Division, Washington, DC 20231

Name: Joyce M. Hezlewski

Date: Sep. 9, 1998

Assistant Commissioner for Patents
Application Processing Division
Washington, D.C. 20231

Dear Sir:

RESPONSE TO NOTIFICATION OF MISSING REQUIREMENTS UNDER U.S.C. 371IN THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US)

This is in response to the "Notification of Missing Requirements Under U.S.C. 371" mailed on August 28, 1998 having a response due by September 28, 1998, which indicated that the signatures of the inventors on the Declaration for the subject patent application are missing. A copy of the above-identified "Notice to File Missing Parts" is enclosed.

Submitted herewith is a Declaration and Power of Attorney for the subject patent application which has been fully executed in compliance with 37 C.F.R. 1.497(a) and (b).

The Commissioner is hereby authorized to charge $130.00 handling fee to Deposit Account No. 19-0091, as well as any fee which might be necessary in connection with the handling and prosecution of the above-identified case. A **duplicate** copy of this sheet is enclosed.

Respectfully submitted,

Date: Sept. 9, 1998

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09/16/1998 PVOLPE 00000048 190091 09077817
01 FC:154 130.00 CH

09077817 091498

DECLARATION AND POWER OF ATTORNEY FOR UNITED STATES PATENT APPLICATION

__X__ Original _____ Supplemental _____ Substitute

As a below-named inventor, I hereby declare that:

My residence, citizenship and post office address are given below under my name.

I believe I am an original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled:

IL-13 RECEPTOR

the specification of which

_____ is attached hereto.

_____ was filed on _____ as United States Application Serial No. _____

_____ and was amended on _____ (if applicable).

__X__ was filed on November 7, 1996 as PCT International Application No. PCT/FR96/01756

__X__ and was amended under PCT Article 19 on April 16, 1997 (if applicable).

I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge my duty to disclose information of which I am aware which is material to the examination of this application in accordance with Section 1.56 of Title 37 of the Code of Federal Regulations.

I hereby claim foreign priority benefit under Section 119 (a) - (d) of Title 35 of the United States Code of any foreign application(s) for patent or inventor's certificate or of any PCT application(s) designating at least one country other than the United States identified below and also identify below any foreign application(s) for patent or inventor's certificate or any PCT application(s) designating at least one country other than the United States filed by me on the same subject matter and having a filing date before that of the application(s) from which priority is claimed:

Country	Number	Filing Date	Priority Claimed Yes	Priority Claimed No
France	95/14424	06 December 1995	X	

I hereby claim benefit under Section 120 of Title 35 of the United States Code of any United States application(s) or PCT application(s) designating the United States identified below and, insofar as the subject matter of each of the claims of this application is not

disclosed in said prior application(s) in the manner provided by the first paragraph of Section 112 of Title 35 of the United States Code, I acknowledge my duty to disclose material information of which I am aware as defined in Section 1.56 of Title 37 of the Code of Federal Regulations which occurred between the filing date of the prior application(s) and the national or PCT filing date of this application:

Application Serial No.	Filing Date	Status

3 — I hereby appoint Mary P. Bauman, Reg. No. 31,926; Michael D. Alexander, Reg. No. 36,080; and Paul E. Dupont, Reg. No. 27,438, or any of them my attorneys or agents with full power of substitution and revocation to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

SEND CORRESPONDENCE TO:

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Malvern, PA 19355

DIRECT TELEPHONE CALLS TO:

MICHAEL D. ALEXANDER

Telephone No. (610) 889-8802

I hereby declare that all statements made herein and in the above-identified specification of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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